WHY TEENS TAKE RISKS...

A Neurocognitive Analysis of Developmental Changes and Individual Differences in Decision-Making under Risk.

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1.

General introduction

1.1 The scope of this thesis

This thesis aims to gain insight into risky behavior in adolescence by contributing to our knowledge about the development of decision-making skills in relation to brain development. Adolescence is a fascinating period in life. In a relatively short period of time, roughly between 10 and 20 years of age (Dahl, 2004; Spear, 2000), children transform into adults. This transformation has implications for the way teens look and behave, and for their cognitive and psychosocial functioning. Adolescents are often characterised as impulsive and prone to take risks. Already at the beginning of the 20th century G. S. Hall, who is often regarded as the founder of adolescent psychology, described an increase in risky behavior and sensation seeking in adolescence. He saw adolescence as a period of "storm and stress"; characterized by conflict with parents, mood swings, and impulsive behavior (Hall, 1904). Similarly, more recent studies show that adolescents report a greater need for sensation seeking compared to children and adults (Arnett, 1996; Zuckerman, 1994), and that more teens than children or adults end up in emergency rooms because of (traffic) accidents, or because of problems related to experimentation with drugs or alcohol (Furby & Beyth-Marom, 1992; Steinberg, 2004). While the consequences of adolescent risk-taking can be grave, most children pass through adolescence relatively calmly (Arnett, 1999; Dahl, 2004; Masten et al., 1999). Nevertheless, during adolescence many decisions are made that will have long term consequences; smoking for example, often starts during adolescence, and adolescents' choices with regards to their education can have consequences in adulthood. These possible negative consequences underline the

importance of understanding the developmental changes that characterize adolescent risky behavior.

Even though the development of risk-taking behavior has been studied from different perspectives, and using different methods (for an extensive review see Boyer, 2006), the stereotypical adolescent risky behavior has been difficult to capture in experiments. The development of non invasive neuroimaging techniques such as Magnetic Resonance Imaging (MRI) and *functional* MRI (fMRI) have enabled us to study structural and functional brain maturation in children, adolescents and adults in vivo. These techniques have transformed both our understanding of the neurological changes that occur during adolescence and the way in which we think about adolescent development. Neuroimaging data can reveal age related changes in brain function, which are not always apparent based on behavioral measures. When combined with behavioral experiments, the ability of these imaging techniques to increase our understanding of the development of risk-taking behavior is promising. However, because this approach is new, many questions still need to be answered. In addition to behavioral measures (accuracy, choice and reaction time data), we used measures of heart rate changes and fMRI to gain insight into the development of the neural correlates of decision-making during development. In the absence of differences in behavior, these measures can reveal age related differences in the processes that underlie this behavior. The remainder of this chapter will give a short overview of the theoretical background of the studies that are presented in this thesis.

1.2 Imaging the developing brain

The results from a large scale longitudinal study on the structural development of normal developing brains in which 145 healthy children and adolescents ranging in age from 4 to 22 years participated revealed a more protracted developmental trajectory than was previously thought. Important changes still take place throughout adolescence (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2004). Even though the overall size of the brain of a 9-year-old is comparable to the size of an adult's brain, there are important differences in brain structure. MRI studies have shown that gray matter volume, or the total amount of neurons and connections between neurons, follows an inverted U shaped developmental trajectory (Giedd et al., 1999). The number of neurons and connections increases from birth on and reaches

a peak at the beginning of adolescence; from this point on the amount of gray matter will decrease. The adolescent brain begins to change, neurons and connections that are not necessary disappear, and important connections are strengthened, allowing the brain to function more efficiently. In contrast, the volume of white matter, which is made up of myelin that supports communications between neurons, shows a linear increase which continues into adulthood (Giedd et al., 1999). Importantly, the rate at which the brain matures differs between brain regions (Shaw et al., 2008). Regions in the prefrontal cortex (PFC) and parietal cortex are among the last regions in which gray matter volume reaches its peak. These regions continue to change throughout adolescence, which is much later than was previously thought (Casey et al., 2005; Gogtay et al., 2004; Sowell et al., 2004).

In addition to these measures of structural brain maturation, the emergence of fMRI has enabled us to see the brain in action. fMRI's high spatial resolution has vastly increased the ability to map cognitive functions on different brain regions. Importantly, because healthy children and adolescents can participate in fMRI studies, hypotheses about the relation between brain development and cognitive development could be tested. The first developmental fMRI studies revealed that children and adults recruit similar brain regions when they perform cognitive tasks (Casey et al., 1995; Thomas, 1999; Nelson, 2000). Functional brain development mirrors structural brain development, and follows a different developmental trajectory in different regions. Brain regions associated with basic (motor and sensory) processes mature before regions associated with more complex cognitive processes (for a review see, Casey et al., 2005). While children and adults recruit similar brain regions, the way in which these regions are recruited changes with development. That is, brain activation seems to reflect more efficient processing with development (Casey et al. 2005). For example, some studies have found activation in prefrontal brain regions that are associated with a specific task in adults to increase with development, suggesting that these regions are engaged more with age (Crone , Wendelken, Donohue, Van Leijenhorst, & Bunge, 2006; Klingberg et al., 2002; Kwon, 2002). In addition, other studies have found that with development activation in brain regions that are not correlated with task performance decreases (Casey et al., 1997, 2000; Durston et al., 2006; Luna, 2001). Because cognitive functions map onto similar brain regions across development, age related differences in the patterns of brain activation can help gain

insight into developmental changes in cognitive processes that underlie age related changes in behavior. Even when participants from different age groups show similar behavior, the patterns of brain activation associated with this behavior can differ. Because of this, fMRI holds the potential to reveal differences between children, adolescents and adults in experimental tasks of decision-making in the absence of behavioral differences in risk-taking. Differences in brain activation patterns between children and adolescents from different ages may provide insight into the seemingly conflicting findings from observation and experimental studies on risk-taking in adolescence.

1.3 Examining decision-making development to understand risk-taking

While studies using self-report and observation methods report a peak in risk-taking and sensation seeking in adolescence (Arnett, 1996; Furby & Beyth-Marom, 1992; Steinberg, 2004; Zuckerman, 1994), studies using experiments have provided almost no evidence of this peak. In contrast, the results from these studies generally show a decrease in risk-taking from childhood to adulthood (Boyer, 2007). It has been argued that during development learning to avoid excessive risks is one of the most important skills that has to be acquired (Byrnes, 1998; Boyer, 2007; Garon & Moore, 2004; Steinberg & Scott, 2003). An influential approach to the study of human behavior in risky or uncertain situations is the study of decision-making. In this thesis, decision-making is defined as the process of choosing between competing courses of action. Often these choice alternatives are associated with possible undesirable consequences, and therefore involve risk. These undesirable consequences can range from mild (e.g. not winning 5 cents in a gambling task) to severe (being in a traffic accident). Decision-making is a complex construct and age-related changes in numerous cognitive abilities contribute to its development. This thesis will focus on the development of three abilities that are requirements for mature decision-making. *First*, the probabilities of positive and negative outcomes associated with a risk have to be judged. *Second*, the potential negative consequences of a risk have to be weighed against the potential benefit associated with it given these probabilities. And *Third,* to allow behavior to be oriented towards reaching long term goals, impulses have to be controlled, or cognitive control has to be applied.

The development of these three abilities has been studied by developmental psychologists, using different experimental paradigms. The literature on the development of the ability to judge probabilities shows mixed results. Piaget and Inhelder argued that children are unable to use probability information in their decisions until they reach the stage of formal operations around early adolescence (Piaget and Inhelder, 1975). However, the results of more recent studies suggest that well before puberty children, as young as 5 years old, have at least a basic understanding of probabilities, and can use this information when making decisions (Acredolo, O'Connor, Banks & Horobin, 1989; Schlottmann, 2001). In contrast, the ability to weigh short-term rewards against long-term rewards has been shown to improve throughout adolescence (Crone & Van der Molen, 2004; Hooper, Luciana, Conklin & Yarger, 2004) in studies in which participants were asked to complete age appropriate versions of the Iowa Gambling Task (IGT). The IGT is a widely used neuropsychological task that simulates real-life decision making in the way rewards, punishments and future consequences of decisions need to be considered. Young children's behavior has been shown to be primarily driven by the magnitude of immediate rewards (Crone & Van der Molen, 2004). In sum, the behavioral literature to date suggests that in straightforward risky situations children as young as 5 years of age can accurately estimate risks when making decisions, but decision-making in more complex situations increases gradually during development, which suggests that mature decision-making emerges over the course of adolescence. With age, participants are more able to choose the behavior that is most advantageous in the long run and focus on their long term goals.

Cognitive control, refers to the cognitive processes that enable us to control our behavior and perform goal-directed actions. It encompasses processes such as working memory (WM), inhibition, and selective attention. Cognitive control has been shown to improve with age (Eigsti et al., 2006; Mischel, Shoda & Rodrigues, 1989), and has been shown to continue to mature during adolescence (Davidson, Amso, Anderson & Diamond, 2006; Diamond, 2002; Huizinga, Dolan & Van der Molen, 2006). It is associated with late maturing brain regions in the prefrontal and parietal cortex (Casey, Galvan & Hare, 2005), and an influential view in the literature on the development of risk-taking behavior suggests that the increase in cognitive control over the course of childhood and adolescence, enables an increase in the ability to make

decisions and control impulses. As a consequence, the development of cognitive control would lead to a decrease in risk-taking with age.

1.4 The insufficient cognitive control hypothesis of adolescent risk-taking

Adolescents' immature cognitive control abilities have been proposed to underlie their impulsivity, risky behavior, and sometimes seemingly irrational decisions. For example, the ability to reject an immediate reward (such as chatting with friends on MSN) in favor of a larger but delayed reward (getting a good grade because you did not chat with friends but did your homework) develops slowly. This ability begins to develop in pre-school aged children. In a classic series of experiments Mischel et al. gave 4 year olds a small reward (e.g. a cookie or marshmallow), and told them that they would receive another reward (an additional cookie or marshmallow) when they managed not to eat the cookie until the experimenter, who left the room for 15 minutes, would return. When 4 year old children are faced with this choice between a small immediate reward, and a larger, more desirable reward, many (approximately 70%) are unable to wait (Mischel et al., 1989). Similarly, when given a choice between a small immediate reward, and a larger delayed reward, children are more likely to prefer the delayed reward with age. This increase in the preference for larger delayed rewards and the ability to wait for rewards has been reported until adolescence (Scheres et al., 2006). The ability to delay gratification at age 4 appears to be predictive of inhibition abilities (Eigsti et al., 2006), and school performance (Shoda, Mischel & Peake, 1990). Children who are more able to control themselves at an early age perform better in adolescence. Several studies have shown that the ability to resist the need for immediate reward improves throughout adolescence (Crone & Van der Molen, 2004; Garon & Moore, 2004; Hooper et al., 2004; Overman et al., 2004). Indirect neuroscientific support for this theory comes from developmental fMRI studies on cognitive control abilities which show that brain regions associated with cognitive control are among the last to mature (Casey et al., 2005). In adults, damage to PFC regions, that are implicated in cognitive control, has been shown to result in impaired decision-making (e.g. Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel & Damasio, 2000). Taken together these findings suggest that immature cognitive control, as a consequence of the protracted development of PFC brain regions contributes to immature decision-making, and possibly to adolescent

risky behavior. However, few fMRI studies examined the role of these PFC regions in the development of risk-taking directly. The studies that did have not included children; May et al. (2004) examined the neural correlates of decision-making in a group of adolescents, and Ernst et al. (2005) and Bjork et al. (2004) compared adolescents to adults. However, these studies focused on brain regions that were implicated in the processing of rewards, not on regions associated with cognitive control. A limitation of the insufficient cognitive control account of risky behavior is that it would predict that children, who have the least mature reasoning skills and cognitive control abilities, should show *even more* risk-taking behavior than adolescents. This would be in contrast to the self-report data which suggest an increase in risk-taking in adolescents compared to children. Therefore, the cognitive control hypothesis can only account for the change in behavior that occurs with the transition from adolescence to adulthood, but cannot explain why risk-taking would increase from childhood to adolescence. A second view explains adolescent risky behavior not as a consequence of the ability to control behavior, but emphasizes the increased sensation-seeking that has been reported by adolescents.

1.5 The increased arousal hypothesis of adolescent risk-taking

Adolescence can roughly be subdivided into two phases; the beginning of adolescence is marked by the onset of puberty around 10 years of age and lasts until about 15 years of age. During puberty the physical transformation from child to adult occurs under the influence of gonadal hormones; children undergo growth spurts and the secondary sex characteristics develop (Spear, 2000; Dahl 2004). The second phase of adolescence follows puberty and lasts until approximately 20 years of age. This phase is characterised by the maturation of psychological and psychosocial abilities (Steinberg, 2005). While physical changes are most apparent during puberty, important developmental changes in both brain structure and function take place throughout adolescence. Biological and physiological changes that start at the onset of puberty have been proposed to underlie the increase in sensation seeking and risky behavior in adolescence. At the onset of puberty gonadal hormones influence the brain, especially neurotransmitter systems in brain areas that are important for the processing of rewards (Spear, 2000). These areas are part of the brain's limbic system which is implicated in the experience of excitement, arousal and emotions (Nelson, Leibenluft, McClure & Pine, 2005). When these regions are

more sensitive to appetitive stimuli in adolescents, this would make them more sensitive to the potential benefits associated with a risk, and as a consequence, adolescents would be more willing to try something new, and explore their environment. On the one hand, this gives them the opportunity to develop skills they need as adults (Kelley et al., 2004), but on the other hand leaves them vulnerable to risks. Because these hormonal changes are specific to adolescence, the increasing emotion and arousal hypothesis predicts a non linear pattern of risk-taking behavior, with a peak in adolescence, which is consistent with the findings from self-report and observation studies.

One of the first developmental imaging studies focusing on adolescent risk-taking examined adolescents in a guessing task in which participants could win money by guessing whether a playing card would be higher or lower than five (May et al., 2004). This study reports more activation in the ventral striatum (VS) and orbitofrontal cortex (OFC) in response to rewards compared to losses. While the May et al. study did not include adults, the VS had previously been shown to play an important role in processing rewards and in motivating behavior in adults (Knutson, Adams, Fong & Hommer, 2001; McClure, Berns, Montague, 2003). Similar findings have been reported by Ernst et al. (2005). In this study activation of brain regions associated with the processing of gains and losses was compared between adolescents and adults in a decision-making task. The VS response to rewards was larger in adolescents than adults. Together these findings suggests that reward related regions in the brain are more activate in adolescence, and this supports the hypothesis that adolescents take more risks because they are more sensitive to the potential benefits associated with that risk. In contrast, a study by Bjork et al. (2004) reported the opposite pattern. In this study reward processing was examined in adolescents and adults in the context of a monetary incentive delay task. Adolescents showed less activation in the VS in response to rewards compared to adults. These authors explained the increase in sensation seeking and risky behavior in adolescence as a consequence of this diminished sensitivity of reward systems. According to these authors, adolescents need more exciting experiences to achieve the same sense of reward as adults, and therefore take risks. It could be that differences in the behavioral requirements between the tasks used in the studies reported above account for differences in the observed patterns of brain activation. Adolescents' risk-taking behavior could be influenced by differences in the strategies used by participants from different ages when they approach a risky

situation. For example, the task used by Bjork and colleagues was more difficult compared to the tasks used by May et al (2004) and Ernst et al. (2005), in that it required more cognitive control. Taken together, these findings show that we cannot explain adolescent risk-taking when we study the development of reward related brain regions, or neuroimaging results in isolation. The studies described in this chapter suggest that in order to fully understand adolescent risky behavior the development of risk estimation, reward processing, cognitive control and age related changes in brain regions associated with these functions should be studied separately, and once it is possible to investigate how these processes can be isolated, it is important to examine how they work together.

Real-world adolescent risk-taking behavior is sometimes extreme and potentially fatal, but usually more subtle. Most adolescents engage in more accepted forms of risky behavior, such as listening to loud music, wearing "extreme clothing", engaging in dangerous sports, or studying for a test at the very last minute. In addition to experiments that can capture subtle age related differences in risk-taking in the scanner, fMRI studies require testable hypotheses on the development of the neural correlates of cognitive processes that underlie the changes observed in behavioral ad self-report studies. The studies discussed in this chapter form a starting point to tackle these questions.

1.6 Outline of this thesis and publications

This chapter has given an overview of the theoretical background of the studies that are presented in this thesis. The six chapters that report empirical studies (Chapters 2-7) aimed to examine the developmental trajectory of decision-making, in order to gain insight into risky behavior in adolescence. Chapters 2 and 3 describe two developmental fMRI experiments that each focus on the neural correlates of cognitive processes that are considered basic components of decision-making under risk; the ability to judge probabilities (Chapter 2), and reward sensitivity (Chapter 3). **Chapter 2** describes the first fMRI study that examined age differences in brain activation patterns in control related regions, between children and young adults (9-12 and 18-26 years old) in a decision-making context. In this chapter we introduce a new child friendly two-choice decision-making paradigm; "the Cake Gambling Task". **Chapter 3** describes a second developmental fMRI study in which neural responses between early adolescents, middle adolescents,

and young adults (10-12, 14-15, and 18-25 years old) were studied in response to rewards. This study examined the hypothesis that adolescence is characterised by a peak in the brain's responsiveness to rewards, and aimed to resolve conflicting findings of earlier studies.

While these first two chapters each focus on one of the processes that underlie decision-making; Chapters 4, 5 and 6 describe experiments in which these processes were combined and participants had to weigh risks against potential rewards. **Chapter 4** describes a behavioral study on the development of decision-making under risk, using a modified version of the Cake Gambling Task that was introduced in Chapter 2. Children, adolescents and adults from five age groups (8-9, 11-12, 14-15, 17-18, and 25-30 years old) participated in this study, in which both the probability of winning and the size of the reward that could be gambled with were manipulated. The results from this study motivated the experiments described in Chapter 5 and 6, in which we examine the relative contributions of reward sensitivity and cognitive control to decision-making under risk. In the study described in **Chapter 5** we used behavioral and psychophysiological measures to test the hypothesis that adolescent decision-making is biased towards taking risks because of an increased sensitivity to possible rewards paired with immature cognitive control. Adolescent participants from three age groups (11-12, 14-15, and 17-18 years-old) were included, and the Cake Gambling task was modified to enable us to measure heart rate changes. In addition, we introduced monetary rewards. **Chapter 6** describes the third developmental fMRI study in which we directly test the hypothesis that brain regions associated with reward processing and cognitive control follow different developmental trajectories, and underlie adolescent risk-taking. Children, adolescents and young adults from 4 age groups (8-10, 12-14, 16-17 and 19-26 years old) gambled for monetary reward in an adapted version of the Cake Gambling Task. In addition, this study examined the relation between brain activation patterns and individual differences in risk-taking behavior.

The final empirical chapter does not focus on decision-making directly. **Chapter 7** focuses on the development of an important cognitive control component, and describes a behavioral study on the development of working memory for object and spatial information in children, adolescents and young adults (6-7, 9-10, 11-12 and 18-26 years old). In addition to behavioral measures this study describes measures of heart rate changes, which provide an index of covert

cognitive processes. Finally in **Chapter 8** the findings described in the empirical chapters are summarized and discussed.

All empirical chapters that this thesis consists of have been published in, or submitted to peer reviewed journals, to acknowledge the contributions of the co-authors the full references to these papers are presented below:

Van Leijenhorst, L., Crone, E. A., & Bunge, S. A. (2006). Neural correlates of developmental differences in risk anticipation and feedback processing. *Neuropsychologia, 44,* 2158-2170. (Chapter 2)

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A. R. B. & Crone, E. A. (*in press*) What motivates the adolescent? Brain regions mediating reward sensitivity in adolescence. *Cerebral Cortex.* (Chapter 3)

Van Leijenhorst, L., Westenberg, P. M. & Crone, E. A. (2008) A developmental study of risky decisions on the Cake Gambling Task; Age and gender analyses of probability estimation and reward evaluation. *Developmental Neuropsychology, 33,* 179-196. (Chapter 4)

Van Leijenhorst, L., Westenberg, P. M., Crone, E. A. (*manuscript in revision*) A heart rate analysis of risky decision-making, reward sensitivity and outcome monitoring in adolescence. (Chapter 5)

Van Leijenhorst, L., Gunther Moor, B., Op de Macks, Z. A., Rombouts, S. A. R. B., Westenberg, P. M., & Crone, E. A. (*manuscript in revision*) Adolescent risky decision-making: neurocognitive development of affective and control regions. (Chapter 6)

Van Leijenhorst, L., Crone, E. A. & Van der Molen, M. W. (2007). Developmental changes in object and spatial working memory: A psychophysiological analysis. *Child Development, 78,* 987-1000. (Chapter 7)

Chapters 1 & 8 are based on a book chapter and paper (in Dutch) that were published as:

Van Leijenhorst, L. & Crone, E. A. (2009). Paradoxes in adolescent risk-taking. In: Zelazo, P. D, Chandler, M. & Crone, E. A. (Eds). *Developmental Social Cognitive Neuroscience.* Oxford University Press.

Van Leijenhorst, L. & Crone, E. A. (2009). Het adolescentenbrein: Inzichten in risicovol gedrag in de adolescentie uit de cognitieve neurowetenschappen. *Neuropraxis, 1,* 3-7.

2.

Neural correlates of developmental differences in risk estimation and feedback processing

The primary aim of this study was to compare the neural substrates of decision-making in middle-aged children and adults. To this end, we collected fMRI data while 9-12-year-olds and 18-26-year-olds performed a simple gambling task. The task was designed to tap two important aspects of decision making: risk estimation and feedback processing. We examined how orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) contributed to risk estimation, and how ventrolateral and medial prefrontal cortices (VLPFC and medial PFC) contributed to negative feedback processing in children and adults. Region of interest analyses revealed differences in brain activation between children and adults for ACC and lateral OFC. ACC was recruited more for high-risk than for low-risk trials, and this difference was larger for children than for adults. In contrast, children and adults did not differ in activation for OFC or DLPFC. These data suggest that children's decision-making under uncertainty is associated with a high degree of response conflict. Both age groups exhibited bilateral VLPFC (BA 47) and medial PFC/ACC (BA 6/ BA 32 (dorsal) and 24 (ventral)) activation associated with negative feedback processing. Relative to adults, children engaged lateral OFC more strongly for negative relative to positive feedback. These results indicate that children may find negative feedback more aversive than adults do. In summary, children aged 9-12 and adults recruit similar brain regions during risk-estimation and feedback processing, but some key differences between the groups provide insight into the factors contributing to developmental changes in decision-making

.2.1 Introduction

Decision-making, which involves the ability to choose between competing actions that are associated with uncertain benefits and penalties, is a key component of human cognition and behavior. Throughout childhood, we learn and develop the ability to make choices that are beneficial in the long run. The ability to make decisions that require the delay of gratification to receive a larger reward in the future begins to emerge during the pre-school period (Mischel, Shoda and Rodriguez, 1989). Interestingly, the ability to delay gratification at age four was found to be predictive of socially competent behavior in adolescence (Mischel et al., 1989). Even though four-year-olds can choose delayed over immediate rewards (e.g., Thompson, Barresi, & Moore, 1997; Prencipe & Zelazo, 2005), children show difficulties with delay of gratification that may persist into adolescence on tasks in which one must make a decision between immediate and future reward (e.g., Hooper , Luciana, Conklin & Yarger, 2004; Crone & Van der Molen, 2004; Overman, 2004). Thus, the ability to make advantageous decisions under conditions of uncertainty does not fully develop until early adulthood.

The mechanisms underlying developmental changes in decision-making are not well understood. The interpretation of behavioral findings is difficult because of the complexity of many decision-making tasks. For example, most decision-making tasks not only require an estimation of risk (Critchley, Mathias & Dolan, 2001), but also require participants to process performance feedback (O'Doherty, Critchley, Deichmann & Dolan, 2003), and keep an appropriate strategy on-line (Barraclough, Conroy & Lee, 2004). Developmental changes have been observed in all of these functions, namely risk estimation, feedback monitoring, and strategy (or task-set) maintenance. Behavioral data indicate that children and adolescents make more disadvantageous decisions, suggesting that they are prone to risk-taking (Overman, 2004; Crone et al., 2003). Additionally, when it is necessary to learn from external feedback, young children are more likely than older children to perseverate in their behavior, which suggests that they may also be less able to use the informative value of performance feedback than older children and adults in order to change their behavior (Kirkham & Diamond, 2003). Finally, a large body of evidence indicates that there are developmental improvements in the ability to keep relevant information online (e.g. Diamond, 2002; Casey, Giedd & Thomas,

2000; Barcelo, 1999; Thomas et al., 1999; Barcelo & Knight, 2002). Thus, to learn more about the factors contributing to developmental changes in decision-making, it is necessary to examine how separable cognitive functions contribute to the complex process of decision-making.

Our understanding of the processes underlying decision-making in adults has benefited from investigations of its neural underpinnings. Brain imaging techniques are especially valuable when overt behavior is difficult to interpret, because different underlying mechanisms may contribute to observed differences in behavior (see Casey, Davidson & Rosen, 2002; Van der Molen & Molenaar, 1994). Neuroimaging studies in healthy adults and neuropsychological studies in patients with real-life decision-making problems have shown that two key components of decision making – risk estimation and processing performance feedback – are subserved by different regions within the prefrontal cortex (PFC) (e.g., Bechara, Damasio, Damasio & Anderson, 1994; Rolls, 2000; Breiter, Aharon, Kahneman, Dale & Shizgal, 2001; Knutson, Adams, Fong & Hommer, 2001; Ernst et al., 2005; Cohen, Heller & Ranganath, 2005). More specifically, these studies show that orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are important for risk anticipation, whereas ventrolateral PFC (VLPFC) is engaged when participants receive negative performance feedback.

In several patient studies, Bechara et al. (Bechara et al., 1994; Bechara, Tranel, Damasio & Damasio, 1996; Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel & Damasio, 2000) have shown that patients with OFC damage make disadvantageous choices on the Iowa Gambling Task. The Iowa Gambling Task mimics real-life decision-making, in that it features immediate and future rewards and punishments. These studies showed that healthy control participants learned to make advantageous choices over the course of the task, favoring larger gains in the future over smaller but more immediate gains, whereas OFC patients selected only those options that result in immediate reward. These findings have been taken as evidence that OFC subserves risk estimation by generating autonomic responses, but that it does not subserve feedback processing. More recent studies have suggested a somewhat different account of OFC function, by showing that OFC patients make disadvantageous choices on the Iowa Gambling Task only when reversal learning is required – i.e., when they must learn to adjust their responses after the reinforcement values of stimuli

have been reversed (Rolls, 1999; Maia & McClelland, 2004, 2005; Fellows & Farah, 2003, 2005). Both accounts, however, suggest that OFC is important for learning to make decisions by weighing possible outcomes (risk estimation).

A number of imaging studies have implicated OFC in decision-making under conditions of uncertainty (Breiter et al., 2001; Paulus et al., 2001; Ernst et al., 2004; Cohen et al., 2005; Ursu & Carter, 2005). Some studies suggest that OFC is important for risk estimation (Cohen et al., 2005; Ursu & Carter, 2005). Additionally, some studies suggest that OFC is responsible for processing negative performance outcomes (Breiter et al., 2001; Elliott, Friston & Dolan, 2000; Kahn et al., 2002; Rogers et al., 1999). However, the anterior, ventral portion of VLPFC (BA 47), which is sometimes considered to be part of lateral OFC, is more consistently reported as being related to receiving punishment feedback (O'Doherty, Kringelbach, Rolls, Hornak & Andrews, 2001; O'Doherty, Critchley, Deichmann & Dolan, 2003; Rogers et al., 2004).

In addition to OFC, several other regions, including anterior cingulate cortex (ACC) and midbrain regions (in particular, the nucleus accumbens and ventral striatum), are reported as being important for uncertain decision-making (Galvan et al., 2005; Rodriguez, Aron & Poldrach, 2005; Cohen et al., 2005; Critchley et al., 2003; Paulus, Hozack, Frank & Braun, 2002; Rogers et al., 2004; Volz Schubotz & Von Cramon, 2003). ACC is associated with the detection of response conflict and the monitoring of performance (Carter et al., 1998; Ernst et al., 2004; Gehring & Knight, 2000; Holroyd, Nieuwenhuis, Mars & Coles, 2004; O'Doherty, Kringelbach, Rolls, Hornak & Andrews, 2001; Van Veen & Carter, 2002). Midbrain regions are thought to be associated with the prediction of errors (Rodriguez et al., 2005) or responsive to the magnitude of reward (Galvan et al., 2005).

Adaptive decision-making requires not only emotional evaluation, but also the weighing of positive and negative consequences of several potential actions. Therefore, it is not surprising that dorsolateral PFC (DLPFC), a region associated with response selection (e.g. Bunge, Hazeltine, Scanlon, Rosen & Gabrieli, 2002b; Critchley et al., 2001; McClure, Laibson, Loewenstein & Cohen, 2004; Rowe, Toni, Josephs, Frackowiack & Passingham, 2000), and working memory requirements of decision-making tasks (Bechara, Tranel & Damasio, 1998; Manes et al., 2002; Fellows & Farah, 2005), is active when subjects make rational

decisions, such as when they decide to wait for future rewards (Fellows & Farah, 2005; McClure et al., 2004). The framework provided by these studies in adults allows us to investigate specific hypotheses regarding developmental changes in decision-making.

Recent advances in developmental neuroimaging have made it possible to relate changes in prefrontal activity to the development of cognitive functions. fMRI studies of cognitive control have reported activation in similar brain regions for middle-aged children and adults (eg. Bunge, Dudukovic, Thomason, Vaidya & Gabrieli, 2002a; Casey et al., 1995; Casey et al., 2000; Klingberg, Forssberg & Wessterberg, 2002; Casey et al., 2002). Interestingly, even though children show activity in similar regions, the pattern of activation often differs between children and adults, suggesting that the development of cognitive functions is related to a refinement in the organization or efficiency in the recruitment of the prefrontal cortex (Casey et al., 2002). Relative to cognitive control, decision-making has received considerably less attention in the developmental neuroimaging literature (see Happeney, Zelazo & Stuss, 2004). To date, only three studies have examined decision-making in adolescents and adults (Bjork et al., 2004; May et al., 2004; Ernst et al., 2005), and no fMRI studies have yet examined decision-making in children under the age of 12.

The present study compares the neural substrates of decision-making in 9-12 year-olds and young adults, using a children's gambling task designed to tap two important aspects of decision making: risk estimation and feedback processing. Because the current fMRI study is the first to investigate decision-making in children, we have chosen to adapt for children a paradigm designed by Critchley et al. (2001) for use in adults. The *cake task* allows us to examine developmental differences in subcomponents of decision-making, including risk estimation and feedback processing. The stimuli in this task resemble “wheels of fortune” that have been used in the adult neuroimaging literature (e.g., see Breiter et al., 2001; Ernst et al., 2004).

In our child-friendly task, the stimuli represent cakes that are part chocolate-flavored and part strawberry-flavored. Participants are asked to look at a given cake stimulus, and decide whether a piece of chocolate or strawberry cake is most likely to be randomly selected by a computer. The proportion of chocolate/strawberry pieces differs between cakes, resulting in low-risk decisions (for example, one

chocolate piece and eight strawberry pieces) and high-risk decisions (for example, four chocolate pieces and five strawberry pieces). Performance feedback, indicating gain or loss, follows each decision.

This study focused on the contributions of OFC, ACC, DLPFC, and the midbrain to risk estimation in children and adults, as well as the contributions of VLPFC and medial PFC to feedback processing. Such a region-of-interest (ROI) approach allowed us to examine changes across development in the relative contribution of these regions to decision-making. Additionally, we examined the extent to which children and adults rely on the same or different brain regions during risk estimation and feedback processing. We focused primarily on negative feedback, because of its importance in updating behavior, but examined the neural correlates of positive > negative feedback as well.

We had two predictions about the development of decision-making. The first prediction was that children have difficulty anticipating risks because the network relying on prefrontal cortex (DLPFC and OFC) and its connections with ACC is not fully developed yet. Such a finding would be consistent with the literature showing that children do not experience warning signals in gambling tasks in a similar way as adults do (e.g., Hooper et al., 2004; Steinberg, 2005). We expected that adults would engage OFC and ACC (e.g., Cohen et al., 2005) as well as DLPFC (McClure et al., 2004) more for high-risk than low-risk decisions. If children exhibit immature risk estimation, we would expect them to exhibit less activation of OFC (associated with affective judgements) and more ACC activation (associated with detection of response conflict), compared to adults. However, if children differ from adults in the way they make rational judgements, we would expect to see less DLPFC (control) and more ACC (conflict) activation.

The second prediction was that children would differ from adults with respect to the impact of negative and positive feedback on their behavior. We expected that if children were to differ from adults in feedback processing, negative feedback would result in a different pattern of neural activity for children than for adults. This finding would be consistent with the literature showing that children fail to process negative feedback (e.g. Kirkham & Diamond, 2003) or process this feedback less efficiently (Crone & Van der Molen, 2004). We expected that adults would engage OFC (Breiter et al., 2001), VLPFC (in particular BA 47), and medial PFC when processing negative vs.

positive feedback (e.g., O'Doherty et al., 2003; Holroyd et al., 2004. If children experience the negative outcomes of their decisions differently from adults, we would expect to find a different pattern of OFC, VLPFC, and medial PFC activation related to loss or punishment feedback in children compared to adults.

2.2 Method

2.2.1 Participants

Twenty-six paid volunteers participated in the study. These participants consisted of fourteen right-handed, healthy young adults (nine females; ages 18-26; mean age = 21.5, SD = 2.2) from the University of Davis and twelve right-handed, healthy children (seven females; ages 9-12; mean age = 11. 3, SD = 0.9). The primary caregiver of each child gave informed consent. Participants' consent was obtained according to the declaration of Helsinki (BMJ 1991; 302: 1194), and the study was approved by the Internal Review Board at the University of California at Davis.

2.2.2 Task

Participants learned to perform the cake task prior to scanning. Each trial started with a 500 ms fixation cross, followed by a stimulus that was presented for 3500 ms, followed by a feedback stimulus that was presented for 2000 ms (see Figure 2.1). The stimulus consisted of a round cake presented at the center of the screen, made up of 9 wedges, each of which were either said to be chocolate-flavored (brown wedges) or strawberry-flavored (pink wedges), followed after 2000 ms by the presentation of a question mark and a piece of strawberry and chocolate cake at the foot of the cake (Figure 2.1). At this point, participants were instructed to indicate by a left or right button press which flavor – strawberry or chocolate – the computer would be most likely to select, given the fact that its choice was random. To ensure that the youngest participants would understand this instruction, all participants were told to think of the computer as someone who picks a piece of cake with their eyes closed. The proportion of strawberry/chocolate wedges varied across stimuli, resulting in low-risk decisions (cakes composed of 9 pieces, of which 1 or 2 pieces had contrasting flavor) and high-risk decisions (cakes composed of 9 pieces, of which 3 or 4 pieces had a contrasting flavor) (see Critchley et al., 2001). Participants used the

middle and index fingers of their left hand to respond. The valence of the feedback participants received always was the consequence of the combination of the computer's random choice for either strawberry or chocolate and the subject's decision. If these two matched, subjects received positive feedback (gained one point), if they didn't match, subjects received negative feedback (lost one point).

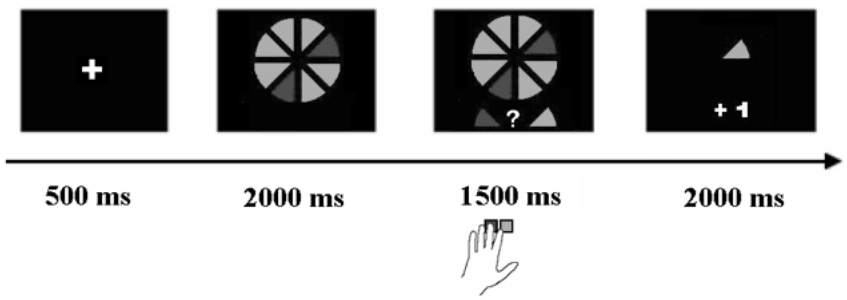

Figure 2.1 *Task example of a low-risk trial. Participants viewed the cake for 2000 ms, followed by the cue and target. Participants had 1500 milliseconds to give a response, after which gain or loss feedback was presented for 2000 ms, along with the choice of the computer. Gain was indicated by +1 and loss was indicated by -1.*

2.2.3 Data acquisition

Over the course of three event-related scans, participants performed a total of 162 experimental trials, in which high-risk and low-risk trials were intermixed. The visual stimuli were projected onto a screen that participants could see via a mirror attached to the head coil. During each scan, subjects performed 27 trials for each risk condition (54 trials total). Across the two scans, there were equal numbers of trials of each type requiring left-button and right-button responses. The order of trial types within each scan was determined with an algorithm designed to maximize the efficiency of recovery of the BOLD response (Dale, 1999). For each condition, the order in which the stimuli were presented was pre-randomized and was the same for all participants. Periods of fixation lasting between 2 and 8 s, jittered in increments of 2 s, were interleaved with the experimental trials, as determined by the optimization program.

Scanning was performed with a standard whole-head coil on a 1.5 Tesla GE scanner at the UCD Imaging Research Center. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2 sec, TE = 40 ms, 24 oblique slices, 3.44 x 3.44 x 5 mm, 0-mm inter-slice

gap, 240 volumes per run). The first four volumes of each scan were discarded to allow for T1-equilibration effects. High-resolution T1 weighed anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head. All children were trained in a mock scanner at the UCD Imaging Research Center prior to the actual scan.

2.2.4 fMRI data analysis

Data were pre-processed using SPM2 (Wellcome Department of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cosoco, Kollokian, Kwan & Evans, 1997), an approximation of Talairach space (Talairach & Tourneaux, 1988). Functional volumes were spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed on individual subjects' data using the general linear model in SPM2. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. The cue and feedback portions of each trial were modeled as single events in two separate models: one event-related design time-locked with the cue presentation, and one event-related model time-locked with feedback presentation. Both designs included four conditions: high-risk positive feedback, high-risk negative feedback, low-risk positive feedback, and low-risk negative feedback trials. Error trials, defined as those trials where the participant did not make the choice that was most likely to result in gain, were modeled separately and were excluded from the fMRI analyses. The correct trial functions were used as covariates in a general linear model, along with a set of cosine functions that high-pass filtered the data, and a covariate for session effects. The least-squared parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. The resulting contrast images, computed on a subject-by-subject basis, were submitted to group analyses. At the group level, contrasts between conditions were computed by performing one-tailed

t-tests on these images, treating subjects as a random effect. Task-related responses were considered significant if they consisted of at least five contiguous voxels that exceeded an uncorrected threshold of $p < .001$, unless reported otherwise.

We employed a fast event-related design in the interest of keeping the study as short as possible for the children. As such, it is likely that risk estimation effects were confounded by feedback effects and *vice versa*. Additionally, a consequence of the way participants tend to perform the task is that negative feedback occurs more often following high risk than following low risk choices, and vice versa for positive feedback. Consequently, any effect of negative feedback could be influenced by the uncertainty associated with high risk trials. For these reasons, our analyses were performed on a selection of trials, to eliminate the effect that the stimuli may have. The comparison of high- versus low-risk decisions was based only on trials followed by positive feedback, thereby holding feedback constant. Similarly, the comparison of positive and negative feedback was based on high-risk trials only, thereby holding risk anticipation constant.

ROI analyses were performed to characterize rule sensitivity of five *a priori* predicted regions – OFC, VLPFC (BA 47), DLPFC medial PFC/ ACC, and midbrain – based on contrasts for risk taking and feedback-processing separately. Averaging the signal across voxels, as is done in ROI analyses, captures the central tendency and tends to reduce uncorrelated variance. Thus, ROI analyses have greater power than whole-brain statistical contrasts to detect effects that are present across a set of voxels. ROI analyses were performed with the Marsbar toolbox in SPM2 (Brett, Anton, Valabregue & Poline, 2002; http:// marsbar.sourceforce.net/). ROIs that spanned several functional brain regions were subdivided by sequentially masking the functional ROI with each of several anatomical Marsbar ROIs. Two contrasts were used to generate functional ROIs: high-risk vs. low-risk trials (risk analysis), and negative vs. positive feedback trials (feedback analysis). These contrasts were generated from all participants with an F-threshold of $p < .001$. An ROI of ACC was identified from the risk analysis, and VLPFC and medial PFC ROIs were identified from the feedback analysis. Additionally, if an *a priori* ROI was active for a contrast in only one of the two age groups, this region was selected to test for significant differences between groups (DLPFC and OFC for the risk analysis, and OFC for the feedback analysis). In the case of the

midbrain, it was not possible to create an ROI based on either a general or a specific contrast. As such, we created a 15 mm spherical ROI centered on MNI coordinates 0, -15, -9 [x, y, z], on the basis of a study by Aron et al. (2004).

For ROI analyses, effects were considered significant at an alpha of .05. Following correction for multiple comparisons across ROIs (5 in total), all critical effects – i.e., Age Group x Condition interactions, survived when the *p*-value was lowered to $p < .01$ ($p = .05/5$ ROIs).

2.3 Results

2.3.1 Performance

Accuracy was defined as the percentage of choices favoring the option with the greatest likelihood of reward. On average, children and adults performed accurately on ± 91 % and ± 98 % of trials, respectively. A 2 (Age Group) x 2 (high-risk vs. low-risk Condition) ANOVA resulted in a main effect of Age Group (F (1, 24) = 14.63, $p < .001$), showing that children made more errors than adults. There was also a main effect of Condition (F (1, 24) = 26.19, $p < .001$), indicating that participants made more errors on high-risk than low-risk trials. There was a marginally significant Age Group x Condition interaction (F (1, 24) = 3.63, $p = .07$, see Figure 2.2), indicating that children were more prone than adults to make a greater number of errors on high-risk compared to low-risk trials.

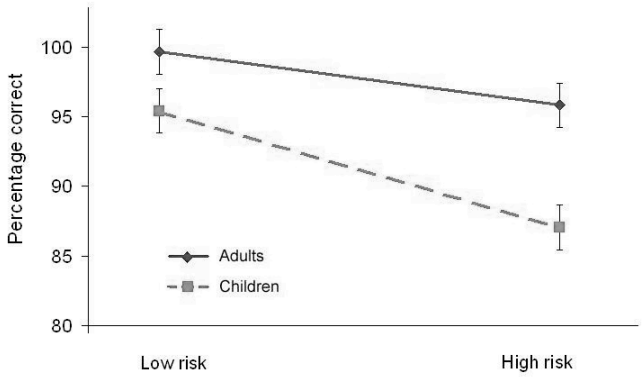

Figure 2.2 *Accuracy for adults and children, for high-risk and low-risk choices. Accurate responses were those trials that were most likely to result in a reward.*

2.3.2 ROI analyses

Risk Estimation

We examined the effects of risk estimation in OFC and DLPFC ROIs derived from the contrast of high-risk versus low-risk in adults. Because these ROIs were defined on the basis of the fact that they were modulated by risk estimation in adults, our analyses focused on whether a similar modulation was also observed in children (Figure 2.3). Both ROI analyses revealed a main effect of Condition, showing that activation was higher in DLPFC (F (1, 24) = 7.80, $p < .01$), and OFC (F (1, 24) = 5.81, $p < .05$) for high-risk compared to low-risk trials, but there were no interactions with Age Group (both F's < 1). The absence of interactions with Age Group suggests that children did not differ from adults in terms of DLPFC or OFC activation on high-risk compared to low-risk trials.

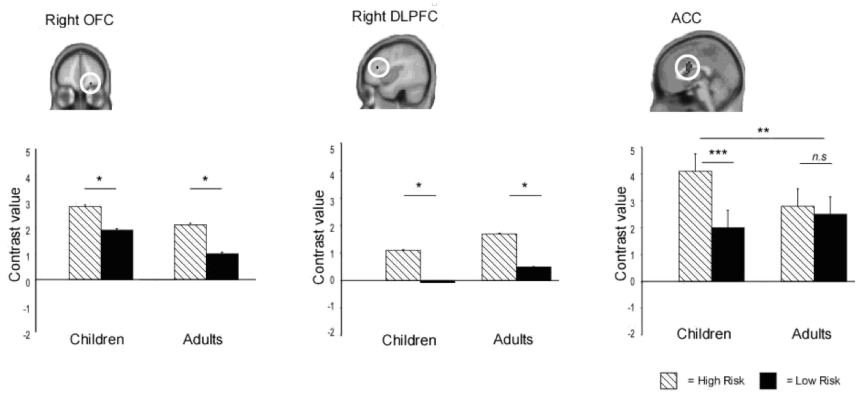

Figure 2.3 *Activation profiles for ROIs derived from high-risk vs. low-risk contrast. The contrast for OFC (22, 50, -14 [x, y, z]) and DLPFC (42, 30, 18 [x, y, z]) was based on a high-risk > low-risk contrast in adults, and the contrast for ACC (0, 6, 20 [x, y, z]) was based on an F-contrast based on all participants.*

We additionally examined the effects of risk estimation in an unbiased ROI of medial PFC/ACC, derived from the F-test of high-risk versus low-risk based on all participants (Figure 2.3). The 2 (Age Group) x 2 (Condition) ANOVA for medial PFC/ACC resulted in a main effect of Condition (F (1, 24) = 14.31, $p < .001$), demonstrating greater activation for high-risk than low-risk trials. This analysis also revealed an Age Group x Condition interaction (F (1, 24) = 5.23, $p < .001$). Post

hoc comparisons for separate age groups showed that children activated medial PFC/ACC more for high-risk than for low-risk trials (F (1, 11) = 10.51, $p < .001$), whereas this difference was absent in adults (F (1, 13) = 2.58, $p = .13$). Thus, children showed greater modulation with respect to risk estimation in medial PFC/ACC than adults, but no age differences were observed in OFC or DLPFC. Finally, an analysis for midbrain was performed for the spherical ROI based on Aron et al. (2004). This region was not influenced by the task manipulations, all p's $> .10$.

Feedback

We performed ROI analyses on medial PFC and right VLPFC (BA 47) regions identified from an F-contrast of negative vs. positive feedback based on all participants. The 2 (Age Group) x 2 (Condition) ANOVA for medial PFC revealed more activity in this region for negative feedback compared to positive feedback (F (1, 24) = 20.16, $p < .001$), but there was no interaction with Age Group ($F < 1$). The same ANOVA for right VLPFC also showed more activity in this region for negative feedback compared to positive feedback (F (1, 24) = 38.06, $p < .001$), but again, there was no interaction with Age Group ($F < 1$). Thus, both children and adults recruited medial PFC and VLPFC more strongly for negative than positive feedback.

An additional ROI analysis focused on the lateral OFC ROI that was derived from the contrast of negative versus positive feedback in children only, and the analysis tested whether this region was also active in adults. The 2 (Age Group) x 2 (Condition) ANOVA resulted in main effects of Age Group, F (1, 24) = 4.87, $p < .05$) and Condition (F (1, 24) = 26.00, $p < .001$), and an Age Group x Condition interaction (F (1, 24) = 10.15, $p < .005$). Post hoc comparisons revealed that both adults (F (1, 13) = 5.95, $p < .05$) and children (F (1, 11) = 17.82, $p < .001$) engaged lateral OFC more strongly for negative compared to positive feedback, but that children showed more activation than adults for negative feedback (F (1, 25) = 5.14, $p < .05$), such that children showed a greater difference between negative and positive feedback than adults did (F (1, 25) = 3.39, $p = .09$).

As noted above, the feedback analysis focused on the comparison between negative and positive feedback in response to high-risk trials only. In the high-risk condition – and even more so in the low-risk condition – positive feedback was more likely to occur than negative

feedback; therefore it is possible that activation for negative > positive feedback is actually related to the feedback being unexpected rather than negative. To examine this issue, we also analyzed positive and negative feedback trials following low-risk trials. If activation associated with negative feedback is related to the feedback being unexpected, then this activation should be larger following low-risk trials, because the probability of negative feedback is lowest in this condition. However, we found no differences in activation for positive and negative feedback trials followed by high-risk trials compared to positive and negative feedback trials followed by low-risk trials (all *F*'s < 1; see Figure 2.4). This result suggests that the negative feedback-related activation is in fact related to the type of feedback provided, rather than to the low frequency of this type of feedback.

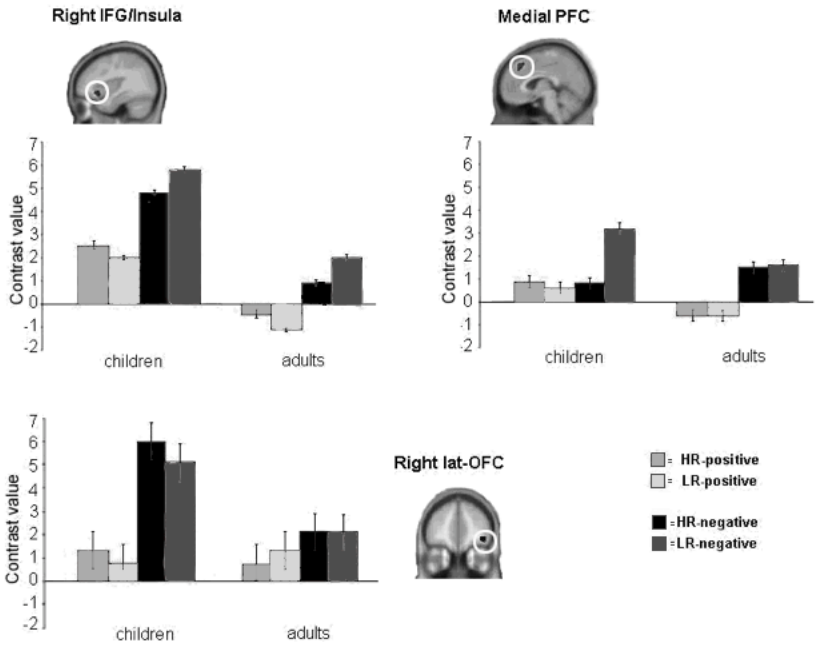

Figure 2.4 *Activation profiles for ROIs derived from gain vs. loss contrast. The contrasts for VLPFC (-20, 12, -20 [x, y, z]) and medial PFC (-22, 18, 50 [x, y, z]) were based on an F-contrast based on all participants. The contrast for OFC (40, 46, -12 [x, y, z]) was based on loss > gain in children.*

2.3.3 Whole-brain analysis

In addition to the ROI analyses, an exploratory whole-brain analysis was performed. These analyses indicate that children and adults showed largely overlapping patterns of activation in the expected brain regions.

Figure 2.5 shows the glass brain images for both comparisons, and Figure 2.6 shows an overlap of the two main comparisons: high-risk > low-risk, and negative feedback > positive feedback.

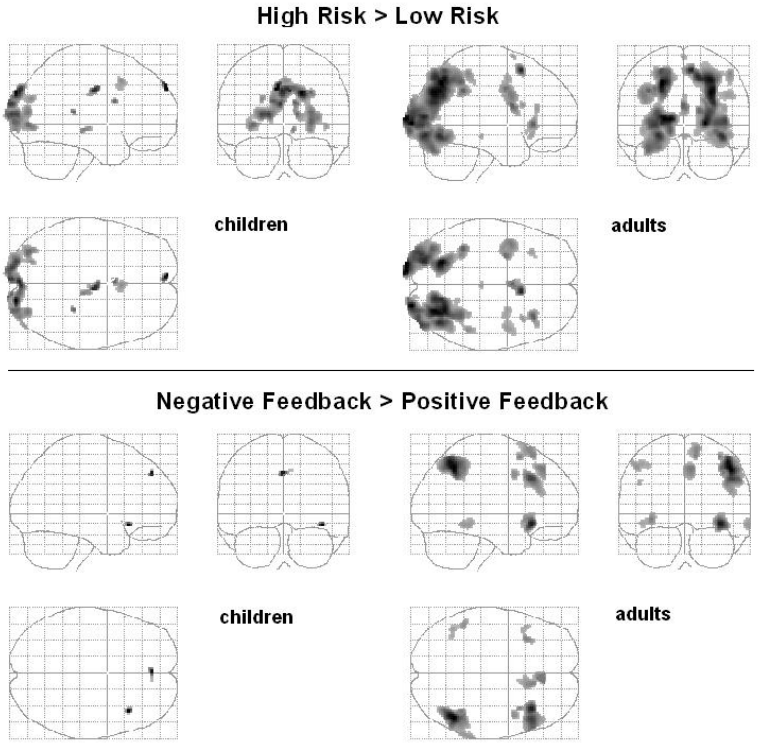

Figure 2.5 *Glass Brain activation profiles for the High-risk >Low-risk contrast and negative > positive feedback contrast in children and adults.*

For the high-risk > low-risk comparison, adults recruited right DLPFC (BA 9), bilateral ACC (BA 24/33), and right VLPFC (BA 47), and children recruited ACC and right VLPFC. When the statistical threshold was lowered to $p < .005$ uncorrected, adults additionally recruited right OFC (BA 11). Additional regions that were active for this contrast are reported in Table 2.1. The results of the reverse comparison (low-risk > high-risk), while not a focus of the current study, are also reported in Table 2.1. For the negative feedback > positive feedback comparison (see Table 2.2), regions activated by adults and children included bilateral VLPFC (BA 47), and medial PFC/ACC (BA 6) at a threshold of $p < .001$ (uncorrected). When the threshold was lowered to $p < .005$ (uncorrected), children additionally recruited a region in right lateral

OFC (BA 11). The reverse contrast (positive > negative feedback, Table 2.1) resulted in a network of regions, including the expected regions for reward processing: bilateral ventromedial PFC (VMPFC) and left caudate nucleus (Knutson et al., 2001; Rogers et al., 2004; O'Doherty et al., 2003). Additional activations are reported in Table 2.2.

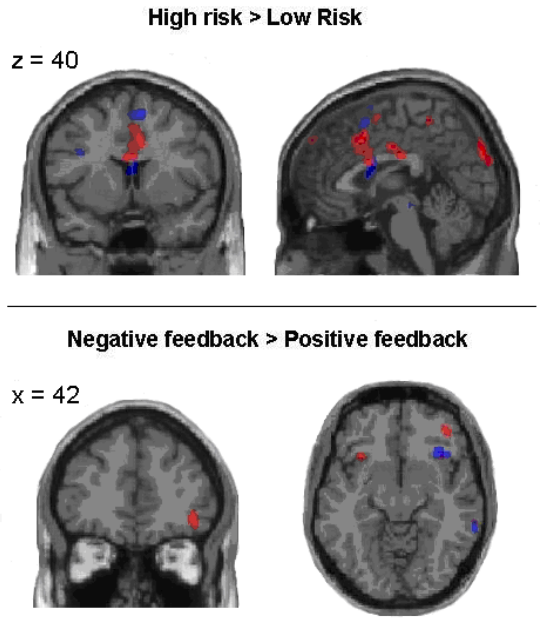

Figure 2.6 *Neural correlates of risk estimation (high-risk followed by positive feedback > low-risk followed by positive feedback), and negative feedback processing (high-risk followed by loss > high-risk followed by gain) in children and adults ($p < .005$). Activation for children is displayed in red, and activation for adults is displayed in blue. High-risk trials were associated with increased medial PFC/ACC activation in both children and adults. Negative feedback trials were associated with increased activation in bilateral VLPFC (BA 47), and children additionally activated right lateral OFC for negative feedback trials.*

2.4 Discussion

In this study, we used fMRI to test whether risk estimation and feedback processing are sensitive to developmental change. We performed ROI analyses to focus on several subregions of PFC that have been associated with these functions in previous studies. Specifically, we examined how OFC, ACC, DLPFC, and midbrain contributed to risk estimation, and how VLPFC and medial PFC contributed to negative

feedback processing. ROI analyses revealed differences in the patterns of brain activation of children and adults in these regions of *a priori* interest, while the whole-brain data indicate overlapping patterns of brain activation associated with risk estimation and feedback-processing for children and adults, suggesting that both age groups performed the task in a similar way. The differences are important, as they provide us with insight into the relative contributions of different brain regions to the development of decision-making abilities. For both risk anticipation and negative feedback processing, we observed greater engagement in both ACC and lateral OFC among children than in adults. These findings suggest that children use these regions less efficiently.

2.4.1 Performance

Children and adults were highly comparable in terms of performance. Importantly, the groups did not differ in performance on low-risk trials, excluding the possibility that children did not understand the task instructions. Participants from both groups tended to choose the option that had the highest likelihood of resulting in reward; thus, few choices resulted in loss (see also Critchley et al., 2001). Both groups, however, made slightly more choices that were likely to result in loss on the high-risk trials, and there was a trend towards a disproportionately larger number of disadvantageous choices on high-risk trials for children compared to adults. These data suggest that, consistent with the literature, children were more prone than adults to take risks on high-risk trials (e.g. Ernst et al.,2005; Overman, 2004). Additionally, response selection demands may have been larger for children on high-risk than low-risk trials, because the perceptual conflict was larger (see Ridderinkhof & Van der Molen, 1995; Bunge et al., 2002a).

2.4.2 Risk estimation

Consistent with our expectations, right OFC (BA 11), bilateral ACC (BA 24/33) and right DLPFC (BA 9) were engaged more strongly when participants made high-risk relative to low-risk decisions. These findings are consistent with previous neuroimaging studies that have shown increased OFC activation when healthy adults make risky decisions (Rogers et al., 2004; Breiter et al., 2001; Ernst et al., 2005; 2005; Ursu & Carter, 2005; Cohen et al., 2005), as well as with non-human primate studies showing that OFC is important for reversal

learning (Schoenbaum, Chiba & Gallagher, 2000; Rolls, 1999; see also Maia & McClelland, 2004, 2005; Fellows & Farah, 2003, 2005), and reward expectation (Tremblay & Schultz, 1999). Contrary to expectations, an ROI analysis targeting the midbrain showed that this region was not affected by the risk manipulation. Parts of the midbrain have been associated with error prediction (Rodriguez et al., 2005), and therefore it was expected to be active in the high-risk condition. However, the results showing that midbrain was not active in this task is consistent with previous studies in which this region has been shown to be sensitive to differences in reward amount (e.g., Galvan et al., 2005), whereas in this study the reward or punishment were always associated with winning or losing one credit.

In summary, children and adults exhibited similar patterns of activation in OFC and DLPFC in relation to risk estimation, but children recruited ACC more strongly for high-risk choices relative to low-risk choices than adults did. The similarities of OFC and DLPFC activation between the groups may reflect the marginal performance differences between children and adults on this simple decision-making task. It would be helpful to manipulate risk level more extensively in future studies – for example, to include trials where the chances of obtaining reward are low but the reward itself is large (e.g., Ernst et al., 2005; Rogers et al., 2004). We predict that excessive risk-taking in children relative to adults would be associated with under-recruitment of DLPFC, a region implicated in the weighing of response options (McClure et al., 2004), and/or under-recruitment of OFC, a region implicated in the anticipation of choice outcomes (Rogers et al., 2004). It should, however, be noted that this was the first fMRI study examining decision-making in children younger than 12 years of age. We have shown that children aged 9-12 recruit many of the same regions that have been linked to risk estimation in adults, albeit with some differences in sensitivity to uncertainty and risk. The sensitivity of these regions to different levels of uncertainty and risk in children should be validated in future research.

Within the current theoretical framework (Ernst et al., 2004; Carter et al., 1998), the finding that children showed greater modulation of ACC for high-risk relative to low-risk choices than adults suggests that children experience greater conflict associated with high-risk trials. ACC is thought to be important for detecting response conflict, monitoring performance, and/or anticipating uncertain outcomes (Bush

et al. 2002; Carter et al., 1998; Critchley, Corfield, Chandler, Mathias & Dolan, 2000; O'Doherty et al, 2001; Van Veen & Carter, 2002). The ACC activation in the present study suggests that performance monitoring for high-risk decisions is more effortful for children compared to adults. This enhanced ACC activation is likely to reflect the fact that children have greater difficulty making the right decision under uncertainty, even if, as in the case of this simple task, they choose advantageously most of the time. Instead or additionally, greater ACC response in children may reflect less efficient performance monitoring in children, even though the high-risk vs. low-risk contrast was estimated purely on the basis of correctly performed trials. Arguing against this interpretation, it has been found that the Error-Related Negativity (a brain potential observed in the encephalogram in response to errors) becomes *larger* over the course of adolescence (e.g. a flanker task in Davies et al., 2004). This latter finding supports the view that children over-recruit ACC on this task because they have greater difficulty than adults in choosing the less risky option.

2.4.3 Feedback processing

Both adults and children recruited bilateral VLPFC (BA 47) for negative vs. positive feedback processing. This result is consistent with previous studies on adults showing that this region is active following punishment (e.g., O'Doherty et al., 2003), and following negative feedback indicating a rule reversal (Cools, Clark, Owen & Robbins, 2002; Cools, Clark & Robbins, 2004). In our study, adults also exhibited activation in medial PFC/ACC (BA 6/ BA 32 (dorsal) and 24 (ventral)). This finding is consistent with previous results by Holroyd et al. (2004), who have suggested that the medial PFC/ACC is active when individuals receive negative feedback as well as when they make an error. However, it should be noted that this interpretation is not universally accepted, and follow-up research by this group has failed to replicate this effect (Nieuwenhuis, Slagter, Alting von Geusau, Heslenfeld, & Holroyd, 2001). Also, the medial PFC region reported here is more anterior than the medial PFC/ACC region reported by Holroyd et al. (2004).

Children additionally recruited a region in right lateral OFC (BA 11) in response to negative versus positive feedback. In adults, this region was only slightly more active following negative than positive feedback, broadly consistent with the view that this region is important for

processing magnitude of both positive and negative outcomes (Breiter et al., 2001). There was no difference between age groups for positive feedback in this region, indicating that right lateral OFC was more strongly attuned to negative feedback for children than adults.

Lateral OFC and VLPFC (BA 11/47) are thought to process negative feedback for the purpose of adjusting behavior to optimize performance (Cools et al. 2002; Kringelbach & Rolls, 2004). In a prior developmental study in which participants had to use performance feedback to improve their performance, we examined how children adjust their behavior based on positive and negative feedback in a stimulus-response mapping task (Crone et al., 2004). On a proportion of the trials, participants received standard response-dependent feedback (i.e., negative feedback after an incorrect response, and positive feedback after a correct response). In a second condition, intermixed with the response-dependent condition and unknown to the participants, participants received positive and negative feedback that was unrelated to their actual performance. Heart rate was measured as an index of feedback processing. In this prior study, we found that heart rate slowed following negative performance feedback, and that the amount of slowing was the same for all age groups for informative feedback. However, participants older than 12 did not show this slowing to *uninformative* negative feedback, whereas children younger than 12 did. These findings suggest that children under the age of 12 have difficulty distinguishing between relevant and irrelevant feedback for the purpose of performance adjustment. Behavioral studies have consistently shown that children perform worse than adults on complex decision-making tasks (Kerr & Zelazo, 2004; Crone et al., 2003; Overman, 2004). This might be in part because they fail to distinguish between informative and uninformative feedback, or because they are less able than adults to adjust their behavior on the basis of negative feedback (Kirkham & Diamond, 2003). The enhanced activation in lateral OFC observed in children in the present study in response to negative feedback suggests that children may be generally more sensitive to negative feedback than adults, regardless of whether or not the feedback is meaningful. This finding could be further investigated in future research by manipulating the magnitude of positive and negative feedback.

2.4.4 Conclusion

These data indicate that the neural correlates of risk estimation and feedback-processing are dissociable in children as well as in adults. First, it is important to note that the children recruited partially overlapping brain regions relative to adults, showing that children aged 9-12 performed the task in a similar way to adults. The differences in the pattern of brain activity (i.e., the relative contribution of the brain regions involved) that were found between 9-12 year olds and young adults, for lateral OFC and ACC in particular, contribute to our understanding of the role that these different processes play in the development of decision-making over childhood.

Table 2.1 *Risk estimation-elicited activation for High-Risk and Low–Risk trials for both age groups*

Contrast	Region	Talairach Coordinates			BA	Z-value	Volume*	Uncorr. p
HR_pos > LR_pos Adults								
Medial PFC	R OFC	22	50	-14	11	2.98		<.005
	R superior frontal gyrus	8	14	56	6	4,37	57	<.001
Lateral PFC	R inferior frontal gyrus	34	28	0	47	3,83	42	<.001
	R DLPFC	42	30	18	46	3.06	160	<.005
	L medial frontal gyrus	-30	-2	38	6	3,61	110	<.001
	L DLPFC	-42	4	32	9	3,49		<.001
Cingulate	L/R ACC	0	6	20	33	3,76	27	<.001
Parietal cortex	R Parietal, precuneus	28	-74	34	19	4,61	2415	<.001
	R superior Parietal	26	-64	46	7	4,53		<.001
	L superior Parietal	-22	-68	44	7	4,67	586	<.001
	L Parietal, precuneus	-20	-74	34	19	3,72		<.001
	R inferior Parietal	48	-40	52	40	3,33	8	<.001
Occipital cortex	L Cuneus	-14	-104	6	18	4,69	1339	<.001
	L Occipital	-24	-86	8	19	4,32		<.001
	L Occipital	-26	-84	-10	18	4,25		<.001
	R Cuneus	22	-98	2	18	4,68	2415	<.001
HR_pos > LR_pos Children								
Medial PFC	R medial frontal gyrus	2	14	44	6	3,44	65	<.001
	L superior frontal gyrus	-8	62	36	9	4,28	24	<.001
Basal Ganglia	R Caudate	28	-34	12		3,69	12	<.001
Cingulate	R Cingulate gyrus	6	-14	34	24	4,06	47	<.001
	R Cingulate gyrus	8	14	36	32	3,25	65	<.001
	L Cingulate gyrus	-2	8	24	24	3,67	22	<.001
Occipital cortex	R Occipital	18	-94	32	19	4,22	1389	<.001
	L Occipital	-2	-90	34	19	4,08		<.001
LR_pos > HR_pos Adults								
Medial PFC	R anterior PFC	16	58	20	10	3,47	16	<.001

Lateral PFC	L Insula	-36	-28	16	13	3,38	10	<.001
Parietal cortex	L inferior Parietal	-66	-32	28	40	4,68	91	<.001
	R inferior Parietal	58	-24	24	40	4,52	145	<.001
Temporal cortex	R Middle Temporal Gyrus	58	-64	8	37	4,05	143	<.001
	L Middle Temporal Gyrus	-58	-68	8	37	3,68	21	<.001
	L Angular	-52	-72	32	39	3,5	71	<.001
Cingulate	R ACC	12	46	-10	29	3,2	5	<.001
Somato-sensory cortex	L Precentral Gyrus	-24	-24	58	4	3,93	63	<.001
Occipital cortex	L Superior Occipital	-46	-80	34	19	3,43	71	<.001
LR_pos > HR_pos Children								
Parietal cortex	L Parietal, Angular	-44	-68	34	39	3,16	5	<.001

HR = high-risk, LR = low-risk, pos = positive feedback,
* Volume of activation in mm^3

Table 2.2 *Feedback -elicited activation (positive > negative and negative > positive) for both age groups*

Contrast	Region	Talairach Coordinates			BA	Z-value	Volume *	Uncorr. p
Negative > positive FB Adults								
Lateral PFC	L IFG	-34	20	-6	47	3,78	78	<.001
	R IFG	36	24	-10	47	4,63	213	<.001
	R DLPFC	48	24	36	9	4,37	447	<.001
	L DLPFC	-46	18	30	9	3,32	14	<.001
	R medial frontal gyrus	36	12	58	6	3,77	22	<.001
	R inferior frontal gyrus	44	6	40	6	3,66	45	<.001
Medial PFC	R superior frontal gyrus	12	26	60	6	3,75	161	<.001
Temporal	R inferior temporal gyrus	64	-46	-12	20	3,53	54	<.001
Parietal	R inferior Parietal	46	-56	48	40	4,86	900	<.001
	L inferior Parietal	-50	-46	48	40	3,59	103	<.001
	L superior Parietal	-44	-58	50	7	3,44		<.001
Negative > positive FB Children								
Lateral PFC	R IFG	40	22	-12	47	3,59	13	<.001
Medial PFC	L medial frontal gyrus	-2	46	42	8	3,53	12	<.001
	R superior frontal gyrus	8	46	44	8	3,12		<.001
	R lateral OFC	40	46	-12	11	2,88	30	<.005
Positive > negative FB Adults								
Medial PFC	R VMPFC	4	50	-10	10	4,9	1598	<.001
	L VMPFC	-4	50	-16	11	4,67		<.001
Lateral PFC	R DLPFC	20	38	18	9	3,62	8	<.001
	L IFG	-20	12	-20	47	4,42	1097	<.001
	L Insula	-34	-42	22	13	3,72	62	<.001
	L Superior frontal gyrus	-22	6	68	6	3,57	28	<.001
	L Medial frontal gyrus	-22	18	50	6	4,18	1079	<.001
	R Medial frontal gyrus	22	28	36	8	3,72	10	<.001
Basal Ganglia	L Caudate	-12	22	4		3,83	1598	<.001
Somato-sensorycortex	R Postcentral gyrus	48	-18	44	3	4,94	3817	<.001
	R Precentral gyrus	66	-4	26	6	4,88		<.001

	R Postcentral gyrus	54	-18	54	3	4,8		<.001
Parietal cortex	L Parietal, sub-gyral	-26	-46	56	7	3,4	16	<.001
Temporal cortex	R Middle temporal gyrus	62	0	-8	21	4,47	325	<.001
	R Superior temporal gyrus	68	-18	0	22	3,83		<.001
	Parahippocampal gyrus	20	-8	-24	35	4,88	3214	<.001
	L Posterior cingulate	-12	-60	14	30	5,04	8525	<.001
	L Middle Temporal gyrus	-48	-76	10	39	4,03	101	<.001
	L Superior Temporal gyrus	-60	-30	14	42	4,22	260	<.001
	L Parahippocampal gyrus	-22	0	-12	34	4,55	1097	<.001
	L Fusiform gyrus	-44	-36	-24	36	3,4	6	<.001
Occipital cortex	L Superior Occipital	-40	-84	36	19	3,98	91	<.001
	L Occipital	-20	-90	40	19	3,74		<.001
Positive > negative FB Children								
Lateral PFC	L Medial frontal gyrus	-20	-2	38	6	3,26	6	<.001
Basal Ganglia	L Caudate	-6	20	8		3,66	5	<.001
Cingulate cortex	R Cingulate gyrus	12	-40	44	31	3,33	10	<.001
Parietal cortex	L inferior Parietal	-66	-26	32	40	3,54	26	<.001
Occipital cortex	L Occipital	-10	-82	20	18	3,23	6	<.001

* Volume of activation in mm^3

3.

What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence

The relation between brain development across adolescence and adolescent risky behavior has attracted increasing interest in recent years. It has been proposed that adolescents are hypersensitive to reward because of an imbalance in the developmental pattern followed by the striatum and prefrontal cortex. To date it is unclear if adolescents engage in risky behavior because they overestimate potential rewards or because they respond more to received rewards and whether these effects occur in the absence of decisions. In this study, we used an fMRI paradigm that allowed us to dissociate effects of the anticipation, receipt and omission of reward in 10-12, 14-15, and 18-23 year-old participants. We show that in anticipation of uncertain outcomes the anterior insula is more active in adolescents compared to young adults, and that the ventral striatum shows a reward related peak in middle adolescence, whereas young adults show orbitofrontal cortex activation to omitted reward. These regions show distinct developmental trajectories. This study supports the hypothesis that adolescents are hypersensitive to reward, and adds to the current literature in demonstrating that neural activation differs in adolescents even for small rewards in the absence of choice. These findings may have important implications for understanding adolescent risk-taking behavior.

3.1 Introduction

Often decisions are made in uncertain situations, in which not all the information needed to make a rational decision is known. When choices in uncertain situations are associated with possible negative outcomes, they are considered risky. An increase in risky behavior is one of the most salient characteristics of adolescence (Arnett 1999; Boyer 2006; Steinberg 2004). This change in behavior suggests a difference in the decision making processes of adolescents compared to adults. That is, adolescents may choose differently between competing courses of action in an uncertain situation, because they weigh the possible outcomes and the probabilities with which these occur differently compared to adults. Prior studies have suggested that adolescents are biased towards taking risks because of differences in the way they experience rewards (Bjork et al. 2004; Ernst et al. 2005; Galvan et al. 2006; May et al. 2004; Van Leijenhorst et al. 2006).

Functional magnetic resonance imaging (fMRI) studies have identified brain regions related to outcome anticipation and processing. Many studies have shown that the ventral striatum responds to anticipation of potential rewards (Breiter et al. 2001; Dagher 2007; Knutson et al. 2001; Tom et al. 2007), which was confirmed by a recent meta analysis (Knutson and Greer, 2008). In addition, the anterior insula have been implicated in the anticipation of outcomes, activation in this region is also often associated with the uncertainty associated with anticipation (Critchley et al. 2001; Volz et al. 2003). Finally, several studies in adults have shown that medial prefrontal, orbitofrontal and anterior cingulate cortex are involved in processing rewards (Bechara 2001; Knutson et al. 2001; O'Doherty et al. 2001; O'Doherty et al. 2002; Rolls 2000).

The functional development of these regions is not well understood. The few developmental studies to date show a seemingly inconsistent pattern of results. Adolescent risk-taking has on the one hand been associated with a *decreased* sensitivity of the ventral striatum to reward in adolescents compared to adults. This neural response has been suggested to lead adolescents to seek more stimulating experiences in order to compensate for low levels of activation in the ventral striatum (Bjork et al. 2004; Spear 2000). On the other hand, adolescent risk-taking has been associated with an *increased* responsiveness of the ventral striatum to reward (Galvan et al. 2006). In these studies, it was suggested that this increase in the response to potential rewards in

combination with immature cognitive control abilities (resulting from the protracted development of the prefrontal cortex (PFC)) biases adolescents towards taking risks (Casey et al. 2008b; Ernst et al. 2006; Galvan et al. 2006).

The interpretation of these developmental findings is complicated for two reasons. First, there is a large variance in the ages of participants that have been included in these studies on adolescent reward processing. This is problematic because adolescents form a very heterogeneous group, for instance, in early adolescence developmental changes could be influenced by pubertal changes. In prior studies adolescents from a broad age range have been included. For example, in the study by (Bjork et al. 2004), the adolescent group consisted of participants aged 12-17-years, which may hinder our interpretation of the pattern of developmental change. Structural brain imaging studies have demonstrated that development of brain structure in terms of grey and white matter proportion continues throughout adolescence (Giedd et al. 1999; Gogtay et al. 2004), and a recent study has shown that these developmental changes follow a nonlinear pattern in many brain regions (Shaw et al. 2008). A second difficulty is that different experimental paradigms have been used in prior reports, making it difficult to compare results. For example, in prior studies rewards were dependent upon participants' task performance, and the requirements for obtaining rewards varied. Rewards could depend on reaction times (e.g. (Bjork et al. 2004), or on response accuracy/ probability matching (e.g. (Ernst et al. 2005; Eshel et al. 2007; Galvan et al. 2006; Van Leijenhorst et al. 2006). In addition, reward magnitude (Bjork et al. 2004; Galvan et al. 2006) reward probability (May et al. 2004; Van Leijenhorst et al. 2006) or both magnitude and probability (Ernst et al. 2005; Eshel et al. 2007) were manipulated. It is therefore difficult to relate developmental differences in ventral striatum activation to risk taking, or reward processing more generally. Recently, studies on adult decision-making have attempted to predict behavior based on preceding changes in activation of the ventral striatum (Knutson et al. 2008a). These studies showed that increased ventral striatum activation is associated with an increased willingness to take risks in adults. In a prior study including adults, Knutson et al. (2008b) used a decision-making task, and presented rewarding pictures that were unrelated to the task. Presentation of these pictures was related to increased activation of the ventral striatum and to increased willingness to take risks (Knutson *et al*. 2008b). Thus, if a peak in activation of the ventral striatum in

adolescents drives them to take risks, it is important to understand the extent to which this region is independent of behavioral requirements. In addition, it is important to understand at what phase, during the anticipation or processing of rewards, differences between adolescents and adults are observed. A better understanding of the causes of adolescent reward processing can help interpret the potentially harmful risky behavior that many adolescents engage in. It is important to understand whether adolescents are more likely to engage in risky behavior compared to adults because they overestimate potential rewards (in an early phase of the decision-making process), or because their response to received rewards differs from that of adults (in a later phase). Insight into these possible differences in reward sensitivity in adolescence informs us about the processes that underlie adolescent real-world risky behavior. In addition this knowledge could aid attempts to intervene and protect adolescents against the problems they face. Basic differences in reward related brain regions between participants form different ages may complicate the interpretation of developmental changes in behavior. One way to work around this difficulty is to study reward processing using an experimental task in which reward and risk are unrelated to participants' behavior (see Tobler et al. 2008) for a similar approach). Therefore, the goal of this study was to examine developmental differences in neural activation related to different phases of reward processing in the absence of behavior.

We compared the neural substrates of outcome anticipation and outcome processing in early and middle adolescence and young adulthood using fMRI. In order to identify the pattern of development of brain regions implicated in the processing of reward we included three homogenous age groups (10-12 year olds, 14-15 year olds and 18-23 year olds). These participants performed a Slot Machine Task (Donkers et al. 2005), a simple paradigm in which small monetary rewards are unpredictable and unrelated to behavior. In this task, participants view three slot machines in which pictures of fruit are presented consecutively. Only when these three pictures are the same, participants win money. The task involves the presentation of three different conditions: 1) all three pictures are different (referred to as the XYZ conditions), 2) the first two pictures are the same but the third is different (referred to as the XXY conditions) and 3) all three pictures are the same (referred to as XXX conditions). In this way, the paradigm allowed us to dissociate brain activation associated with outcome anticipation (when the first two out of three pictures are the same versus

all three pictures are different; XXY vs XYZ), processing of reward (when all three pictures are the same versus the first two out of three pictures are the same; XXX vs XXY), and omission of reward (XXY vs XXX).

Our analyses focused on identifying brain regions implicated in reward processing and uncertainty, including the striatum, the insula and the orbitofrontal cortex (OFC). Our first hypothesis was that these regions show functional development which is reflected in a different pattern of activation in the different age groups. We tested for linear and nonlinear developmental patterns. Our second hypothesis was that if adolescent risk taking is associated with increased sensitivity to reward this should be reflected in a peak in activation in the ventral striatum in this age group. We examined at which stage, during anticipation or processing of outcomes, the ventral striatum would show different responses in the absence of behavioral requirements, and whether the response to rewards in this region would be increased or decreased in adolescents compared to adults. The results are expected to provide insight in the development of reward related brain regions during adolescence, and contribute to the interpretation of differences in neural responses between adolescents and adults in more complex reward and risk-taking tasks.

3.2 Method

3.2.1 Participants

Fifty-three healthy, right-handed volunteers participated in the study, fifteen 18-23 year olds (7 females; mean age = 20.2, SD = 1.6), eighteen 14-15 year olds (10 females; mean age = 15.0, SD = 0.7), and seventeen 10-12 year olds (8 females; mean age 11.6, SD = 0.8). Informed consent was obtained from all participants and from a primary caregiver in case participants were younger than 18 years of age. The study was approved by the Medical Ethical Committee at the Leiden University Medical Centre. Data from three additional adult participants were excluded because of technical difficulties. Data for participants who had moved more than 3 mm in any direction were excluded from the analyses. For this reason, the data of three participants (a 14, 15 and 10 year old) were excluded. Average movement was .52 mm for the 18-23 year olds, .68 mm for the 14-15 year olds, and .62 mm for the 10-12 year olds. The

difference in average movement between the age groups was not significant (p >.1).

3.2.2 Behavioral assessment

Prior to scanning, all participants were prepared for the scan session in a quiet laboratory in which a mock scanner was present. This mock scanner, which simulated the environment and sounds of an actual MRI scanner, gave minors the opportunity to become accustomed to the scanner environment, and was used to explain the scanning procedure to all participants. In order tot obtain an estimate of IQ, age appropriate versions of two subtests of the Wechsler Adult Intelligence Scale (Wechsler 1981) or the Wechsler Intelligence Scales for Children (Wechsler 1991) - Similarities and Block Design - were administered to all participants. For 10-12 year olds, 14-15 year olds and 18-23 year olds estimate IQs were 119.7 (SD = 9.7), 106.0 (SD = 9.0) and 108.7 (SD = 9.4) respectively. 10-12 year olds' average IQ was significantly higher relative to the other two age groups (F(2, 49) = 11.62, p =.001) but overall participants' IQs fell in the average range. The analyses reported below were all corrected for differences in IQ by adding IQ as a covariate factor to the analyses. However, none of the effects were influenced by IQ differences. Therefore, IQ differences are not described further.

All participants were screened for psychiatric conditions, drug use, head injuries and contraindications for MRI using a checklist. No participants reported any problems. In addition, participants in the two youngest age groups were screened for behavioral problems using parent-ratings on the Child Behavior Checklist (Achenbach 1991). Scores for all participants fell within the non clinical range.

3.2.3 Experimental Design

Participants performed the Slot Machine Task, a child-friendly version of a paradigm used previously by (Donkers et al. 2005). Each trial started with the presentation of three empty slot machines. After 500 ms, a coin was presented at the bottom of the screen for 1000 ms, which served as a cue. In order to keep participants engaged in the (otherwise passive) task, they were instructed to start the machines by pressing a pre-specified button with their right index finger on presentation of the cue. The response had to be given within a 1000 ms time window.

Following the 1000 ms response window, three pictures, each one of three possible fruit types – a kiwi, a pear or a pair of cherries - were presented consecutively, from left to right in the slot machines, every 1500 ms (See Figure 3.1).

Pictures were presented in three possible orders: 1) three different pictures (e.g., kiwi-pear-cherries, referred to as XYZ trials), 2) two identical and one different picture (e.g., kiwi-kiwi-cherries, referred to as XXY trials) or 3) three identical pictures (e.g., kiwi-kiwi-kiwi, referred to as XXX conditions). These three trial types represent three experimental conditions. The order in which trials were presented was randomized and participants were presented with a new combination of the three pictures on each trial. Participants were instructed in advance that they would gain € 0.05 on each XXX trial, and that they would not gain money on the other types of trials. When participants failed to respond during the 1000 ms. cue presentation, the trial ended and they received a € 0.10 penalty. This occurred on less than 5% of the trials. At the end of the experiment the total winnings (€ 1.50) were added to the amount that participants received as reimbursement for participating in the study.

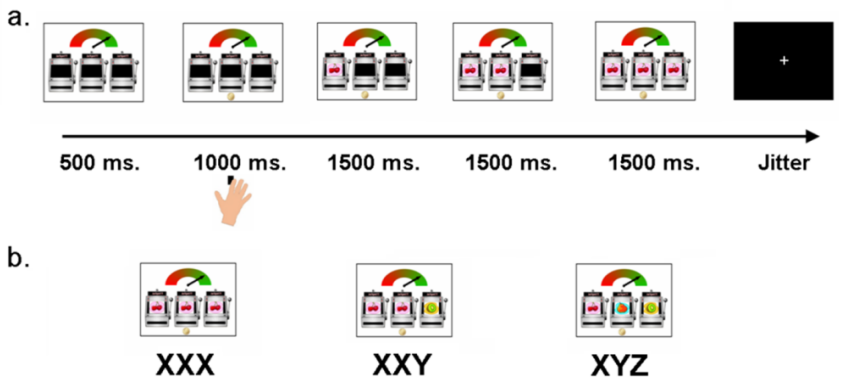

Figure 3.1 *Example of a.) a trial, b.) a possible outcome displays for the Slot Machine Task. Following a 1000 ms. time window in which participants could respond to the cue, three pictures appeared consecutively every 1500 ms. resulting in three trial types: XXX, XXY or XYZ. Participants won € 0.05 on each XXX trial, and did not win in the other conditions.*

3.2.4 MRI Data Acquisition

Trials were presented over the course of two event-related scans that each lasted approximately 7 minutes. The visual stimuli were projected

onto a screen that participants could see via a mirror attached to the head coil. During scanning participants were presented with a total of 120 trials, in which XXX, XXY and XYZ trials were intermixed, such that 60 XYZ trials, 30 XXY and 30 XXX trials were presented in total, with 60 trials in each run. Age related differences in response to rewards could be influenced by slow maturation of the ability to learn probabilities and predict risk. We controlled for this possibility by presenting the three consecutive stimuli in pseudo-random order to maximize uncertainty. On all trials after presentation of the first picture the probability that the next picture in the series of three was the same was always 50%. In the same way, after two identical pictures had been presented the probability that the third picture was the same was 50%. (50% XYZ, 25% XXY, 25% XXX trials, following (Donkers et al. 2005). Periods of fixation lasting between 1 and 3 s, jittered in increments of 500 ms, were added in between the experimental trials.

Scanning was performed using a standard whole-head coil on a 3 Tesla Philips scanner at the Leiden University Medical Center (LUMC). Functional data were acquired using a T2*-weighted gradient-echo echo-planar pulse sequence (38 contiguous 2.75 mm oblique axial slices, using interleaved acquisition, TR = 2.211 s, TE = 30 ms, 2.75 x 2.75 mm inplane resolution, 230 volumes per run). The first two volumes of each scan were discarded to allow for T1-equilibration effects. High-resolution T2* weighed images and high resolution T1 anatomical images were collected at the end of the scan session. Head motion was restricted using a pillow and foam inserts that surrounded the head.

3.2.5 fMRI preprocessing and Statistical analysis

Data pre-processing and analysis was conducted using SPM2 (Wellcome Department of Cognitive Neurology). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Structural and functional volumes were spatially normalized to T_1 and echo planar imaging templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization the data was resampled to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco et al. 1997). Functional volumes were smoothed with an

8-mm full-with at half maximum isotropic Gaussian kernel. Statistical analyses were performed on individual subjects' data using the GLM in SPM2. The fMRI time series were modeled as a series of events convolved with a canonical hemodynamic response function (HRF) in two separate models. We modeled each trial in the three different conditions (XXX, XXY, and XYZ) as a zero duration event around the onset times of the second stimulus in a first model, and around the onset times of the third stimulus in a second model. Error trials, defined as those trials where the participant did not respond within the 1000 ms cue window, were modeled separately and were excluded from the fMRI analyses.

For each participant the parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair wise contrasts. For the first model we computed contrast images for the comparison of XXY and XYZ (i.e. comparing the situation where participants had first seen two pictures that were the same (XX) versus two pictures that were different (XY)); which revealed brain activation patterns related to the *anticipation* of the outcome of trials, based on the hypothesis that adolescents are more sensitive to potential rewards than adults. For the second model we computed contrast images for the comparison of XXX and XXY conditions; comparing brain activation patterns related to the processing of the outcome of trials. The resulting contrast images computed for each participant were submitted to second level group analyses. At the group level, whole brain contrasts between conditions were computed by performing one-tailed t-tests on these images, treating participants as random effect. Whole brain statistical maps were thresholded at $p < .001$, with an extent threshold of 5 contiguous voxels.

3.2.6 Statistical Analyses: Age related differences

Since we were especially interested in the pattern of activation related to outcome anticipation and outcome processing in the three different age groups, we performed voxelwise ANOVAs to identify regions that showed age-related differences in activation. We tested for linear (-1 0 1), quadratic (-0,5 1 -0,5) and curvilinear (1 -0,5 -0,5), (-0,5 -0,5 1) effects in the in the contrasts of XXY - XYZ for the first model (outcome anticipation), and XXX - XXY for the second model (outcome processing). ANOVAs were considered significant at a

statistical threshold of .001 uncorrected for multiple comparisons, with an extent threshold of 5 contiguous voxels.

3.2.7 Imaging Results: Region of Interest Analysis

We used the MARSBAR toolbox for use with SPM2 (Brett et al. 2002) to perform region of Interest (ROI) analyses to further characterize patterns of activation. We created 6 mm spherical ROIs centered at the peak activity voxel in the regions that were identified in the ANOVAs testing for age related differences. In addition we used MARSBAR to extract BOLD activity time series in these ROIs by averaging the time courses for the different experimental conditions starting at the onset of each trial. These time courses are displayed for illustrative purposes in Figures 3.2 and 3.3.

3.3 Results

3.3.1 Outcome Anticipation

We conducted a GLM analysis on the functional data modeled at the onset of the second stimulus, and computed the voxelwise contrast of XXY > XYZ for 10-12-year-olds, 14-15-year-olds and 18-23-year-olds separately. These analyses resulted in largely overlapping areas of activation for the three age groups. In all age groups, outcome anticipation was consistently associated with activation in the right anterior insula (see Figure 3.2 top panel). For 10-12 year olds and 14-15 year olds anterior insula activation was found in both hemispheres. In addition, the adolescent age groups showed activation clusters in the ventral striatum and dorsal cingulate cortex. Significant clusters and corresponding MNI coordinates are reported in Supplemental Table 3.1.

The voxelwise ANOVAs testing for age related changes for the XXY - XYZ contrast did not result in any significant clusters at a threshold of $p < .001$. At a more liberal threshold ($p < .005$) the ANOVA testing for the -1 0 1 contrast revealed a linear change in activation with age in the right anterior insula (peak at: 42, 12, -3, z = 2.95), F (1, 47) = 11.24, p = .002. We created a 6 mm spherical ROI centered at this voxel and performed an Age group (3) x Condition (2) ANOVA on the data extracted from this ROI to further characterize activation patterns in this

region. Average time series for this ROI are plotted in the bottom panel of Figure 3.2. The ANOVA for this ROI resulted in an Age group x Condition interaction, F (2, 47) = 7.00, p =.002. Follow up comparisons confirmed that this region was more active in the XXY compared to the XYZ condition in the 10-12-year-olds F (1, 16) = 11.26, p = .004, and 14-15-year-olds F (1, 17) = 3.62, p = .005. For the 18-23 year olds the difference between conditions was not significant (p = .19).

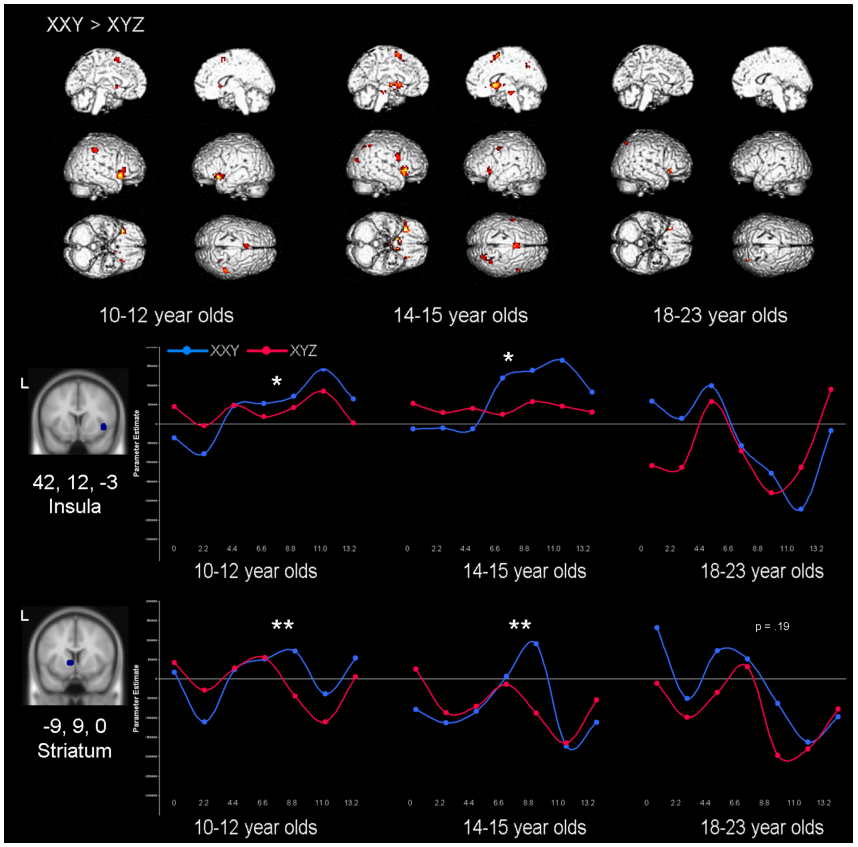

Figure 3.2 *Whole brain results for the 10-12 –year-old, 14-15-year-old and 18-23-year-old participants related to the anticipation of possible reward for the contrast of XXY > XYZ at a p < .001 uncorrected threshold (top panel). And 6 mm spherical ROIs and average time courses for the three age groups for the anterior insula, and striatum (lower panel).*

No age related changes for the XXY - XYZ contrast were found in the striatum. An ANOVA did reveal that this region was active in all age groups (peak at: -9, 9, 0, z = 4.57) in anticipation of outcomes, F (3, 47) = 13.11, p < .001. As anticipated, ANOVAs on the data extracted from the 6 mm spherical ROI for this region resulted in a main effect of

Condition, F (1, 47) = 23.73, p < .001, and no significant interaction with Age Group (p = .1). These results demonstrate that the striatum was more active in anticipation of potential reward to the same extent in all age groups. Nevertheless, comparisons for the age groups separately suggest a larger ventral striatum response in the adolescent groups. That is, in the 10-12 and 14-15 year-olds the XXY condition resulted in significantly more activation compared to the XYZ condition (p's for the main effect of Condition = .001), whereas in adults this difference only showed a trend towards significance (p = .09).

3.3.2 Outcome Processing

To examine brain activation patterns related to the processing of outcomes, a similar GLM analysis was performed on the functional data modeled at the onset of the third stimulus. Again, we computed the contrasts of interest for 10-12-year-olds, 14-15-year-olds and 18-23-year-olds separately. For the contrast of XXX > XXY (reward processing) we found activation in the striatum and dorsal cingulate cortex for 10-12-year-olds and 14-15-year-olds (see Figure 3.3 top panel). No significant clusters were found for the 18-23-year-olds, not even at a more liberal uncorrected threshold of p < .005. 14-15-year-olds also showed activation in left lateral prefrontal cortex.

A GLM for the reverse contrast of XXY > XXX (processing of omitted reward) did not reveal any significant clusters for both the 10-12-year-olds and 14-15-year-olds. In contrast, a region in the left OFC was found to be more responsive to omitted rewards in 18-23-year-olds at an uncorrected threshold of p < .001. An overview of significant clusters and corresponding MNI coordinates are reported in Supplemental Table 3.2.

The voxelwise ANOVAs testing for age related changes for the XXX - XXY contrast confirmed the whole brain findings for the XXX > XXY contrast by showing that activation in the striatum differed between adolescents and young adults. At an uncorrected threshold of p < .001 the ANOVA testing for the -0.5 1 -0.5 contrast revealed a cluster in the ventral striatum (peak at 12, 9, -15, z = 3.68) that showed a quadratic developmental pattern, F (1, 47) = 17.64, p < .001. The Age group (3) x Condition (2) ANOVA on the data extracted from the 6 mm spherical ROI centered at this voxel revealed that his region was more active in the XXX compared to the XXY condition in 14-15-year-olds F (1, 17) =

22.84, $p < .001$, but did not differ between conditions in the 10-12-year-olds ($p = .41$) and 18-23-year-olds ($p = .12$) (see Figure 3.3 bottom panel). The whole brain contrasts for the separate age groups revealed a region in the lateral OFC which was responsive to omitted rewards in the adult group. This finding was confirmed with an ANOVA testing for a curvilinear developmental trend with the -0.5 -0.5 1 contrast that resulted in a region in lateral OFC (peak at: -27, 48, -3, z = 3.05), F (1, 47) = 11.99 $p = .001$ (see Figure 3.3 bottom panel). ANOVAs on the 6 mm spherical ROI for this region resulted in a Condition x Age group interaction F (2, 47) = 8.67, $p = .001$. Follow up comparisons confirmed that this region only showed an increased response to the omission of rewards compared to received rewards in the 18-23-year-olds F (1, 14) = 7.38, $p = .02$.

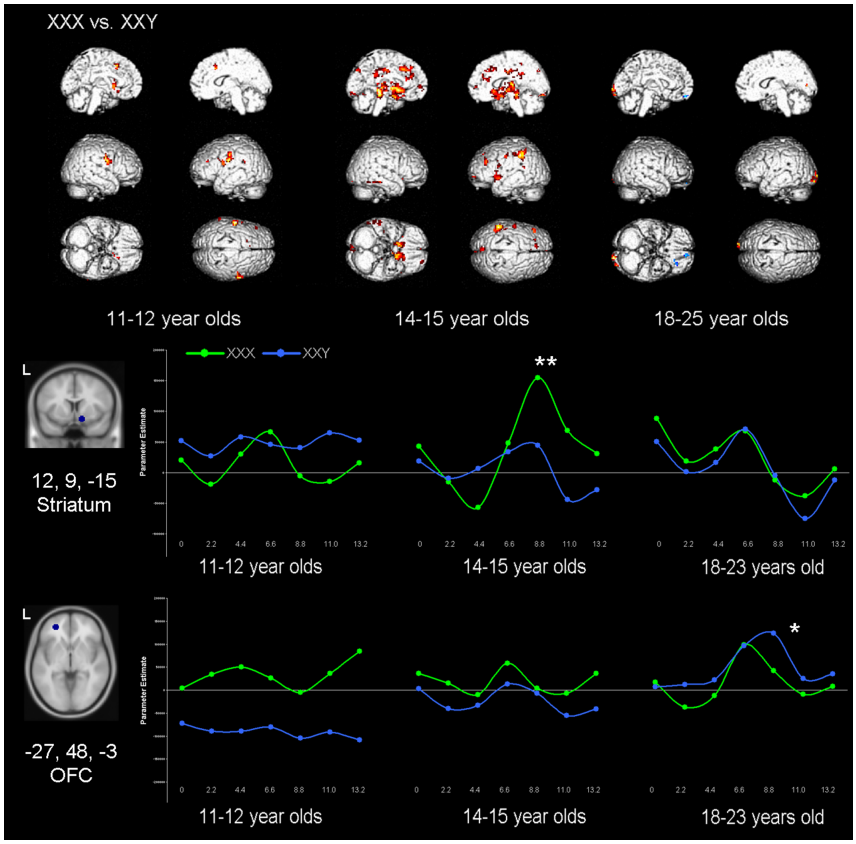

Figure 3.3 *Whole brain results for the 10-12 –year-old, 14-15-year-old and 18-23-year-old participants related to the anticipation of possible reward for the contrast of XXX > XXY at a p < .001 uncorrected threshold (top panel) and XXY > XXX (in blue). And 6 mm spherical ROIs and average time courses for the three age groups for the striatum and OFC (lower panel).*

3.4 Discussion

This study was motivated by the question how adolescents differ from adults in their sensitivity to uncertain reward. We examined the developmental trajectory of brain activation related to the processing of uncertain reward during the anticipation and outcome phases. Prior studies have reported inconsistent findings on adolescent reward processing, showing both *over*active (Galvan et al. 2006) and *under*active (Bjork et al. 2004) incentive-related neurocircuitry in adolescence. The present study differed from these previous studies in that we used a paradigm which resulted in probabilistic reward that was not dependent on behavior. This approach allowed us to examine basic differences in reward sensitivity under uncertainty. In addition, we examined neural differences in three distinct age groups; 10-12-year-olds, 14-15-year-olds, and 18-23-year-olds, which enabled us to test for different patterns of age related change.

The study yielded two main results: 1) when anticipating uncertain rewards, all age groups showed increased activation in the striatum, but a cluster in the anterior insula showed a linear decrease in activation form early adolescence to adulthood. 2) When processing the outcome of trials, middle adolescents were more responsive to received rewards as indicated by increased activation in the ventral striatum, whereas young adults responded most to the omission of rewards as indicated by increased activation in the OFC. In general, our findings support the hypothesis that middle adolescence is characterized by overactive incentive-related neurocircuitry, but we show that this effect is most pronounced during the phase of reward receipt. In light of the results of prior studies these results favor the hypothesis that overactive reward related circuitry and immature PFC circuitry potentially bias adolescents towards taking risks (see also (Casey et al. 2008a; Ernst et al. 2005; Galvan et al. 2006).

3.4.1 Developmental changes in outcome anticipation

Anticipation of outcomes was associated with activation in the striatum and anterior insula when the first two stimuli were identical, and indicated the possibility of winning. Activation in the insula showed a linear decrease with age; this region was most active in 10-12 year olds, less active in 14-15 year olds, and least active in 18-23 year olds when anticipating reward. In the paradigm that we used, the anticipation of

potential reward was associated with maximum uncertainty. After presentation of two of the same pictures, the probability of the third picture being the same or different was equal. In contrast, when the second picture was different from the first, a reward was no longer possible, and as a consequence there was no uncertainty associated with the anticipation of the outcome. The age related change in anterior insula activation could therefore reflect differences in at least two processes: 1) positive arousal associated with the anticipation of receiving a reward, or 2) the uncertainty when anticipating an unknown outcome.

Our results are consistent with the results of recent studies which have implicated the anterior insula in situations where decisions are associated with uncertainty (Huettel 2006; Huettel et al. 2005; Paulus et al. 2003; Volz et al. 2003; Volz and von Cramon 2006). The anterior insula have often been implicated in the experience of psychophysiological arousal. It has been suggested that the insula aid decision making by reflecting the autonomic nervous system responses to risk associated with a decision (Bechara 2001; Critchley et al. 2001; Paulus et al. 2003). Large autonomic signals preceding a disadvantageous decision have been suggested to serve as a warning signal that protect against risk-taking (Bechara et al. 1997). In light of this hypothesis the increased insula response in younger adolescents seems contradictory. However, other studies have suggested that this autonomic signal reflects the salience of the decision that has to be made (Tomb et al. 2002), and prior developmental studies showed that children experience autonomic signals when anticipating risky decisions, but fail to use these signals to optimize their decisions (Crone et al. 2005; Crone & Van der Molen 2004, 2007). In the current study, the increased insula activation in young adolescents could reflect immaturity of this region. The youngest participants could have experienced increased psychophysiological arousal related to the uncertainty associated with anticipation of a possible reward. Even though we did not collect subjective ratings of affect, previous studies have attempted to correlate experienced affect and patterns of brain activation. A recent study found that while activation in the ventral striatum correlated with reported positive affect, activation in the anterior insula correlated with both positive and negative reported affect (Samanez-Larkin et al. 2007). The results from this study suggest that the anterior insula might contribute to decision-making by reflecting general arousal in uncertain situations.

Huettel (2006) dissociated uncertainty related to the amount of potential reward that could be gained (reward risk), and uncertainty with regard to the optimal response (behavioral risk). He showed that activation in the anterior insula was selectively influenced by uncertainty related to response selection. Our results add to this finding by showing that the anterior insula is involved in uncertain situations in the absence of response selection, suggesting that this region may have a more general role in representing uncertainty of outcomes. A recent study (Preuschoff et al. 2008), showed that the anterior insula reflect the degree of uncertainty in a way similar to that in which the striatum is sensitive to the magnitude of reward. The authors suggest that the anterior insula could support processes similar to the reward prediction errors in the striatum. The linear decrease in activation in this region shows that anterior insula function is immature in adolescence, and could be taken to suggest a greater difficulty in adolescents to estimate the risk involved in an uncertain situation. Possibly, adolescents expected reward more often compared to adults in the present study because they did not learn that the occurrence of rewards was unpredictable. Taken together, the increased response in the anterior insula in anticipating an uncertain reward may bias adolescents towards increased risk-taking behavior.

One explanation that has to be considered is that the increased activation in the anterior insula reflects negative affect. Not winning might be associated with more experienced negative arousal when it occurs at the end of the trial (XXY) compared to when it occurs at the presentation of the second picture (XYZ). Even though we estimated the HRF at the onset of the second stimulus, the third stimulus followed 1.5 sec later. Therefore, it is possible that the observed neural response is influenced by the third stimulus. In future studies it will be important to further examine the effect of both the degree of risk/uncertainty and the amount of reward on adolescent decision-making. Given the possible focus of the adolescent group on reward, it would be interesting to test if the neural systems that are responsive to uncertainty respond similarly when the valence of the outcome is negative, i.e. when the XXX condition would reflect a loss rather than gain.

3.4.2 Developmental changes in outcome processing

As expected, winning money resulted in increased activation in the ventral striatum. This finding replicates previous studies that have

shown that this region is responsive to rewards (Huettel 2006; Knutson et al. 2001; McClure et al. 2003). Interestingly, striatal activation following a win peaked in 14-15-year-olds, and was less pronounced in 10-12-year olds, and 18-23-year-olds, consistent with the hypothesis that this region is more responsive in adolescents (Casey et al. 2008a; Ernst et al. 2006a; Galvan et al. 2006).

In the present study, we found the peak in responsiveness of the ventral striatum in middle adolescence only for reward processing, not for reward anticipation. This finding is inconsistent with previous studies, which reported an increase in activation in this region before the actual delivery of rewards. These prior results were taken to suggest a role for the ventral striatum in the prediction and anticipation of outcomes (Bjork et al. 2004; Galvan et al. 2006; Huettel 2006; Knutson et al. 2001). Our findings, however, suggest that the peak in ventral striatum response in adolescents is only found for the receipt of rewards. In previous experiments, the cues signaled potential rewards and allowed for reward prediction, therefore activation in the ventral striatum in these studies could reflect an early response to *knowing* that the reward will follow, rather than anticipating the *possibility* of a reward. These data could also be taken to suggest that adolescents overestimate their chances of obtaining a reward, or ability to obtain a reward. We suggest that in the present study a peak in activation in the ventral striatum was not observed until the actual delivery of reward because the task design maximized uncertainty and did not allow for reward prediction. Even though the anticipation results did not show a statistically significant peak in activation and no Age x Condition interaction in the ventral striatum, follow up analyses hinted that the anticipation striatum response was larger for young and middle adolescents relative to adults. Future studies should study the anticipation versus outcome results in more detail.

Finally, young adults, but not early and middle adolescents, showed increased activation in left lateral OFC following the omission of rewards. Lateral OFC has previously been implicated in processing of punishment (O'Doherty et al. 2001). The OFC is highly connected to both appetitive circuitry and other regions within the PFC, and recently it has been suggested that OFC has an integrative function by guiding the brains' response to affective information, and guiding affective decision making by maintaining and updating a representation of incentive related expectations online (for reviews, see (O'Doherty 2007;

Wallis 2007). The response of lateral OFC in young adults may therefore signal the need for increased attention and adjustment of behavior following negative outcomes. It should be noted that the OFC is a heterogeneous region and many questions regarding its role in goal directed behavior and decision making and associated changes with development need to be tested in future studies. The finding that this region is involved in the processing of unfavorable outcomes in adults, but not in early and middle adolescents, is consistent with the hypothesis that networks in the brain related to higher order processing and cognitive control functions do not mature until late adolescence (Ernst et al. 2006a; Galvan et al. 2006).

3.4.3 Conclusions

The current findings could be interpreted in light of recent accounts that seek a neuropsychological explanation for adolescent behavior. Both the Social Information Processing Network model (SIPN) (Nelson et al. 2005) and the Triadic Model (Ernst et al. 2006) contain an appetitive component and a cognitive/regulatory component. In these models, adolescent behavior is characterized by a strong appetitive system and a relatively weak control system. The SIPN Model (Nelson et al. 2005) suggests that the brain structures that underlie the appetitive component are responsive to gonadal hormones, and are triggered at the beginning of puberty, in contrast to cognitive structures that follow a slower development.

The passive paradigm used in the present study did not allow us to resolve questions about the way in which differences in the neural substrate of reward processing and risk perception between adolescents and adults contribute to motivated behavior in adolescents and adults. It is important to elucidate this relation and its developmental trajectory, because adolescent risky behavior can have serious consequences (Fareri et al. 2008; Steinberg 2004). The finding that reward related brain regions are more responsive in adolescence, even when rewards are unrelated to behavior and small, suggests fundamental differences in the way in which uncertain rewards are processed at different ages. In order to judge the ecological validity of these findings, future studies should take individual differences in for example sensation-seeking, temperament and gender into account and will have to examine these regions using more complex tasks. A second limitation of this study is that we did not obtain direct measures of pubertal status, which limits

our ability to interpret the contribution of pubertal changes to the differences between the 10-12 and 14-15-year-olds. Future studies should attempt to more closely relate age related changes to changes associated with pubertal development.

In summary, our findings demonstrate that brain activation patterns related to outcome anticipation in the absence of behavior are distinguishable from those related to the processing of outcomes. Anticipation of uncertain reward is associated with activation in the anterior insula and striatum. In particular, activation in the anterior Insula shows a linear developmental trend, and decreases from early adolescence to young adulthood. In contrast, processing of reward is associated with a peak in activation in the ventral striatum in 14-15-year-olds, and 10-12-year-olds to a lesser extent. Interestingly, 18-23-year-olds are most responsive to omitted reward, showing activation in lateral OFC regions. These findings support the hypothesis that adolescence is characterized by an imbalance in the maturation of affective and regulatory brain circuitry (Ernst et al. 2005; Galvan et al. 2006; May et al. 2004). The present data show that at a basic level of processing adolescents are more responsive to anticipated and received reward and risk associated with uncertainty compared to adults.

Supplemental Table 3.1 *MNI coordinates of peak activation voxels for significant clusters related to the anticipation of reward (XXY > XYZ contrast) for 10-12, 14-15 and 18-23-year-olds, significant at p < .001 uncorrected.*

Contrast	Region	MNI coordinates			Z-value	Cluster size (voxels)
XXY > XYZ						
10-12-year-olds						
	R anterior insula	36	24	-9	4.67	167
	L anterior insula	-33	18	9	4.23	10
	L anterior insula	-33	15	-15	4.19	90
	L caudate	-6	6	0	3.85	11
	R caudate	12	15	0	3.67	9
	L frontal lobe - Suppl. motor cortex	-3	6	57	3.48	32
	R parietal lobe - Sup. parietal	30	-45	42	3.84	47
	R parietal lobe - Supramarginal gyrus	51	-33	45	3.86	38
	L parietal lobe - Lateral occipital cortex	-27	-60	30	3.30	6
14-15-year-olds						
	R anterior insula	30	27	0	5.18	238
	L anterior insula	-33	15	6	3.74	71
	L ventral striatum - Accumbens	-9	9	-3	4.16	34
	R thalamus	9	0	0	4.52	98
	L thalamus	-6	-9	-3	4.00	27
	R frontal lobe – Paracingulate gyrus	9	15	48	3.44	7
	R frontal lobe – Precentral gyrus	54	9	27	4.01	41
	L frontal lobe – Precentral gyrus	-54	0	45	3.78	13
	R frontal lobe – Suppl. motor cortex	3	3	63	3.93	59
	R parietal lobe – Lateral occipital cortex	24	-66	36	4.33	137
	R occipital lobe – Lat. occipital cortex	30	-78	18	3.84	21
18-23-year-olds						
	R Anterior insula	33	27	0	5.16	35
	L Anterior insula	-33	21	6	3.91	11
	R parietal lobe – Lateral occipital cortex	33	-69	54	3.55	7

Supplemental Table 3.2 *MNI coordinates of peak activation voxels for significant clusters related to the processing of reward (XXX > XXY contrast), and to the processing of omitted rewards (XXY > XXX contrast) for 10-12, 14-15 and 18-23-year-olds, thresholded at p < .001 uncorrected.*

Contrast	Region	MNI coordinates			Z-value	Cluster size (voxels)
XXX > XXY						
10-12-year-olds						
	L frontal lobe – Inferior frontal gyrus	-36	12	27	3.91	10
	L caudate	-12	9	0	3.79	33
	L frontal lobe – Precentral gyrus	-54	-12	42	3.77	79
	R frontal lobe – Precentral gyrus	60	0	24	3.67	62
	L frontal lobe – Precentral gyrus	-54	3	24	3.52	22
	L frontal lobe - Paracingulate gyrus	-3	18	45	3.50	28
	L frontal lobe – Superior frontal gyrus	-18	12	48	3.37	5
	L parietal lobe – Supramarginal gyrus	-63	-45	24	3.35	6
	L putamen	-18	18	-12	3.28	6
	L frontal lobe – Middle frontal gyrus	-42	36	24	3.26	5
14-15-year-olds						
	L caudate	-15	3	21	4.40	283
	L parietal lobe – Supramarginal gyrus	-51	-39	45	4.30	179
	R anterior insula	30	15	-15	4.29	18
	L parietal lobe - Parahippocampal gyrus	-12	-33	-9	4.28	497
	L frontal lobe - Paracingulate gyrus	-6	18	42	4.21	122
	R temporal lobe – Fusiform cortex	39	-21	-15	4.04	5
	L parietal lobe - Posterior cingulate gyrus	-3	-39	27	4.01	130
	L anterior insula	-39	3	-3	3.98	110
	L frontal lobe – Frontal pole	-24	60	-3	3.95	9
	L frontal lobe – Subcallosal cortex	-12	21	-18	3.92	7
	R occipital lobe – fusiform gyrus	15	-87	-15	3.86	41
	L Thalamus	-15	-36	9	3.83	8
	L frontal lobe – Middle frontal gyrus	-42	33	27	3.82	32

	R temporal lobe – Inf. temporal gyrus	57	-30	-18	3.73	24
	L frontal lobe – Paracingulate gyrus	-15	36	24	3.67	24
	R temporal lobe – Inf. temporal gyrus	57	-54	-18	3.63	5
	L occipital lobe – Precuneus cortex	-3	-78	36	3.62	32
	R parietal lobe – Postcentral gyrus	21	-42	54	3.55	6
	L frontal lobe – Precentral gyrus	-51	-9	39	3.53	20
	L parietal lobe – Supramarginal gyrus	-57	-48	15	3.49	6
	R frontal lobe – Anterior cingulate gyrus	3	30	15	3.48	40
	M frontal lobe – Frontal pole	0	57	3	3.45	17
	Cerebellum	0	-63	-15	3.43	7
	M parietal lobe – Post. cingulate gyrus	0	-24	24	3.32	5
18-23-year-olds						
	R occipital lobe – Intracalcarine cortex	15	-81	6	3.67	6
	L occipital lobe – Occipital pole	-15	-102	-3	3.55	32
	L occipital lobe – Occipital pole	-30	-93	-12	3.44	13
XXY > XXX						
10-12-year-olds						
	R temporal lobe – Fusiform cortex	-24	-48	-15	3.64	12
	R parietal lobe – Precuneus cortex	24	-54	6	3.31	5
	L temporal lobe – Fusiform gyrus	-39	-66	-18	3.26	7
14-15-year-olds						
	No significant clusters					
18-23-year-olds						
	L frontal lobe – Frontal orbital cortex	-27	36	-12	4.20	7
	L frontal lobe – Frontal pole	-9	54	-18	3.79	9

4.

A developmental study of risky decisions on the Cake Gambling Task; Age and gender analyses of probability estimation and reward evaluation

Decision-making, or the process of choosing between competing courses of actions, is highly sensitive to age related change, showing development throughout adolescence. In this study, we tested whether the development of decision-making under risk is related to changes in risk-estimation abilities. Participants (N = 93) between ages 8-30 performed a child friendly gambling task, the Cake Gambling task, which was inspired by the Cambridge Gambling Task (Rogers et al., 1999), which has previously been shown to be sensitive to orbitofrontal cortex (OFC) damage. The task allowed comparisons of the contributions to risk perception of 1) the ability to estimate probabilities, and 2) evaluate rewards. Adult performance patterns were highly similar to those found in previous reports, showing increased risk-taking with increases in the probability of winning and the magnitude of potential reward. Behavioral patterns in children and adolescents did not differ from adult patterns, showing a similar ability for probability estimation and reward evaluation. These data suggest that participants 8 years and older perform like adults in a gambling task, previously shown to depend on the OFC in which all the information needed to make an advantageous decision is given on each trial and no information needs to be inferred from previous behavior. Interestingly, at all ages, females were more risk-averse than males. These results suggest that the increase in real-life risky behavior that is seen in adolescence is not a consequence of changes in risk perception abilities. The findings are discussed in relation to theories about the protracted development of the prefrontal cortex.

4.1 Introduction

Decision-making can be defined as the process of choosing between competing courses of actions. Often, the outcomes of decisions we make are uncertain and associated with the possibility of leading to undesirable results, therefore they involve taking risks. Successful decision-making in everyday life situations requires the ability to find a balance between possible benefits and costs that are associated with taking these risks, as well as incorporating the likelihood of achieving what we desire. Decision-making is an important and complex ability that slowly develops during childhood and into adolescence (see Boyer, 2006 for a review). Adolescence in particular has been characterized as a period of increased risk taking (Steinberg, 2004). Self-report and observation studies have shown an increase in, for example, the number of traffic accidents and in the use of illegal drugs, tobacco and alcohol during adolescence (eg. Steinberg, 2004; Furby & Beyth-Marom, 1992). These results suggest that adolescents are not capable of adult decision-making. From a cognitive perspective, many aspects of developmental changes in decision-making abilities are not well understood, even though the possible serious consequences of inadequate decision-making skills in real life make a better understanding important.

In the present study we examined the development of two important abilities that are required for successful decision-making; 1) probability estimation (deciding which choice has the largest chance of resulting in reward) and 2) evaluation of the reward associated with the least likely outcome (does the reward that can be gained make it worth taking the risk). More specifically we developed a child friendly gambling paradigm inspired by the Cambridge Gambling Task (Rogers et al., 1999), the Cake Gambling Task, which specifically taps these two processes.

Recent advances in neuropsychological and neuroimaging research have contributed to the understanding of decision-making abilities in adults. Studies on patients with damage or lesions to the orbitofrontal cortex (OFC) have given insight into the importance of this region for successful decision-making. The OFC is the region of the prefrontal cortex (PFC) which lies at the base of the brain, directly behind our forehead and comprises Brodmann area's 10, 11, 13, 14, and 47/12. Interestingly, damage to the OFC is related to impaired decision-making in real life, while other cognitive abilities remain intact (Bechara et al.,

1994; Bechara, Tranel, Damasio & Damasio, 1996; Bechara, Damasio, Tranel & Damasio, 1997; Bechara, Tranel & Damasio, 2000, Rolls, Hornak, Wade, & McGrath, 1994). A distinctive characteristic of OFC patients is that they fail to perform on reversal learning tasks. In these tasks participants learn to differentiate between a stimulus that is associated with a reward and a stimulus that is not associated with a reward. During the task, the contingencies change, in such a way that the previously unrewarded stimulus becomes associated with a reward and the previously rewarded stimulus is no longer associated with a reward. The previously learned association between a stimulus and a reward has to be unlearned; OFC patients are unable to reverse stimulus-reward associations. As a consequence they fail to modify their behavior when changes in the environment require them to do so (Rolls et al., 1994).

A neuropsychological task which was specifically designed to mimic real-life decision making, the Iowa Gambling Task (IGT), (Bechara, Damasio, Damasio & Anderson, 1994), also demonstrates OFC patients' decision-making deficit. The IGT is an experimentally controlled card game in which participants are instructed to win money by selecting cards from four decks. Two of the four decks result in frequent large gains, but selecting from these two decks is disadvantageous in the long run because of occasional large losses. Selecting cards from the two other decks is advantageous in the long run because even though this choice results in smaller gains, occasional losses are also small. Participants have to learn from the consequences of their choices during the task which decks are advantageous and which they should avoid in order to maximize their winnings. While healthy participants learn to do this over the course of the task, participants with damage to the OFC continue to select from the disadvantageous decks. Neuroimaging studies in healthy adults have confirmed the role of OFC in decision-making and risk-taking (Cohen, Heller, & Ranganath, 2005; Ernst et al., 2002; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006; Rogers et al., 1999).

To our knowledge, most of the behavioral studies on the development of decision-making have used the IGT or child-friendly versions of this task. These studies have shown an increase in performance with age in childhood and adolescence (Crone & Van der Molen, 2004; Hooper, Luciana, Conklin & Yarger, 2004; Kerr & Zelazo, 2004; Overman, 2004). In particular, these studies demonstrate that children aged 6-12-

years select cards mainly from disadvantageous decks, whereas 13-17-year-old adolescents learn to select cards from advantageous decks over task blocks. However, comparison across studies indicates that adolescents do not yet perform at an adult level. These findings indicate that the ability to distinguish between advantageous and disadvantageous decks is still developing in late adolescence (Hooper et al., 2004; Overman, 2004). Children's inability to learn which decks are advantageous resembles that of patients with OFC damage, and has led to the hypothesis that children's behavior on the IGT is related to immaturity of the OFC. This hypothesis is consistent with recent studies on brain development that have shown that the PFC is one of the last areas of the brain to mature structurally, as indicated by age related changes in gray and white matter volumes into early adulthood (Giedd et al., 1999; Gogtay et al, 2004) and functionally, as indicated by functional neuroimaging studies that show different patterns of activation on tasks that recruit PFC in children and adults (eg.Casey et al., 2005; Ernst et al., 2005; Galvan et al., 2006). Behavioral differences between children, adolescents and adults can provide us with a window on the developing brain.

The IGT has been successful in that it closely resembles real-life decision making, and the results of developmental studies that used this task have given us many insights into age related changes in decision-making. Nevertheless, we believe our gambling paradigm can help broaden the insight into the development of different abilities that form the basic building blocks of decision-making. The IGT is a complex task, changes with development have been observed in, for example, the ability to keep, and work with information in working memory, the ability to estimate risks, and the ability to predict, and process the outcome of decisions (Hooper et al., 2004; Kirkham & Diamond, 2003). The developmental trajectories of these abilities and their respective contributions to decision-making are largely unknown. Neuroimaging studies have shown that a network of PFC regions is active when performing the IGT (Ernst et al., 2002), and IGT performance of patients with damage to PFC regions outside of the OFC has also been shown to be impaired (Clark, Manes, Antoun, Sahakian & Robbins, 2003; Bechara et al., 1998).

To address this problem in interpreting the results from developmental studies that used the IGT task or similar tasks, we chose to focus on risk perception in the absence of other processes that contribute to decision-

making. The Cambridge Gambling Task that was developed by Rogers and colleagues (1999) differs from the IGT in that on each trial it gives participants all the information concerning the relative attractiveness of the risky and safe decisions. In the CGT participants are shown six boxes and are told that the computer has randomly selected one of these boxes to hide a token in. Participants are instructed to win as much money as possible by guessing in which box the token is hidden. A proportion of the boxes is red and a proportion is blue, and participants bet on one of these two possible outcome colors. Crucially, a large reward is always associated with the minority color. Importantly, because performance on the task is not dependent on the outcome of previous trials, demands on working memory are low and outcome processing is less important. Therefore this task specifically taps two abilities that comprise risk-perception; the ability to 1) estimate probabilities, and 2) evaluate rewards.

To gain more insight in the developmental pattern of these two abilities, participants ranging in age from 8 to 30, in 5 age groups: 8-9, 11-12, 14-15, 17-18, and 25-30 year olds were included in the present study. The Cake Gambling Task was developed to make the gambling paradigm understandable for young children and to stir their involvement. A simpler version of the Cake Gambling paradigm has previously been shown to be appropriate for use with children in a neuroimaging study that examined probability estimation in children and adults (Van Leijenhorst, Crone & Bunge, 2006). In the current version of the Cake Gambling Task participants are instructed to win as many credits as possible by gambling with two flavors of cake. Two specific manipulations were introduced to dissociate between separable aspects of risk perception. First, three types of cakes which differed in the probability of winning associated with gambling were presented, in order to tap the ability to estimate probabilities. Second, a number of credits that could be won or lost was associated with the choices that could be made. Similar to the Cambridge Gambling Task (Rogers et al., 1999) a large number of credits was always associated with the smallest likelihood of winning, in order to tap the sensitivity to the magnitude of the reward associated with gambling.

The proportion of pink/brown wedges, and the number of credits associated with the colors were varied systematically across trials. On each trial one of the wedges was selected randomly by the computer, according to the different proportions. This selection resulted in a 17%,

33% or 50% chance that the least likely of the two outcome possibilities was selected. For the 17% condition in which both colors were associated with 1 credit, we expected participants to choose the safe decision. This ability was expected to be present already for the youngest participants, because prior research has indicated that the ability to estimate probabilities is already present by age 5 (Schlottmann, 2001). When the number of points associated with the risky decision increased we expected participants to choose this option more often. We expected that the youngest children would be the least risk-averse, and we expected that with age participants became more risk-averse (Boyer, 2006). In addition, we expected that participants would gamble more often when the probability of winning increased, so for the 17%, 33% and 50% chance of winning conditions we expected similar patterns of results, but an increase in gambling (see Rahman et al., 2001).

An additional complication in measuring age differences in decision-making is the variance explained by individual differences. Differences in the tendency towards sensation seeking behavior are likely to contribute to differences in risk-taking (Crone, Vendel & Van der Molen, 2003). Sensation seeking can be defined as "the need for varied, novel, and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experience" (Zuckerman, 1979, p.10). Participants completed a sensation seeking scale to examine correlations between self-report measures of risk-taking and risk-taking as measured with the Cake Gambling task. We expected higher levels of sensation-seeking to be associated with more risk-taking (Lejeuz et al., 2002; 2003). Also, general cognitive abilities might be related to participants' task performance. For this reason, all participants completed the Raven SPM as an index of IQ.

One further variable was taken into account. In prior decision-making studies, gender differences have also been consistently reported (Overman et al., 2004). Interestingly, on the IGT men outperform women, a pattern which is observed in children (Kerr & Zelazo, 2004; Garon & Moore, 2004), adolescents (Crone, 2005; Overman, 2004), and adults (Reavis & Overman, 2001). This finding seems to contradict self-report indices of risk-taking which show that boys and men are less risk-averse than women (for a review see: Byrnes, Miller, & Schafer,

1999). In the present study gender differences were examined to clarify these contradictory findings. By selecting an equal number of men and women in each age group, we could examine whether gender differences may be specifically present in a certain age range.

4.2 Method

4.2.1 Participants

93 volunteers, distributed among five age groups participated in the study: 19 8-9 year olds (M = 9.4, SD = .78, 10 female), 18 11-12 year olds (M = 10.9, SD = .68, 12 female), 20 14-15 year olds (M = 14.6, SD = .51, 10 female), 17 17-18 year olds (M = 17.18, SD = .70, 8 female), and 19 25-30 year olds (M = 27.6, SD = 1.26, 8 female). Chi-square analyses indicated that gender distributions did not differ significantly between age groups χ^2 (4) = 2.49, $p > .05$. Children and adolescents were recruited by contacting local schools. All participants were selected with the help of their teachers; informed consent was obtained from a primary caregiver. Adults were recruited through flyers. In all age groups the participant with the highest score received a small reward.

4.2.2 Cake Gambling Task

Participants completed a computerized child friendly gambling task, the Cake Gambling Task, which was inspired by the Cambridge Gambling Task (Rogers et al, 1999). In this gambling task all information that is relevant for making a decision is presented to participants on each trial and no information has to be learned or retrieved over consecutive trials. On each trial, participants gamble with a round cake presented at the center of the screen. Cakes consisted of 6 wedges that could be brown or pink, and participants were told that these wedges were chocolate-flavored (brown wedges) or strawberry-flavored (pink wedges). A brown and pink square containing a number of coins, indicating the number of credits that was associated with each flavor, were presented at the foot of each cake. The proportion of pink/brown wedges (5:1, 4:2, or 3:3), and the number of credits (1, 3, 5, 7 or 9), associated with the wedges were varied systematically across trials. Importantly, 1 credit was always associated with the most likely of the two outcome possibilities, a *safe choice,* and 1, 3, 5, 7 or 9 credits were always associated with the least likely of the two outcome possibilities,

a *risky choice*. Each trial started with a 500 ms fixation cross, followed by a stimulus that was presented for 5000 ms, followed by a feedback stimulus that was presented for 1000 ms. 3000 ms after the stimulus appeared on the screen, a question mark was presented in between the squares at the bottom of the screen. At this point, participants were instructed to indicate by a left or right button press which color – pink or brown – the computer was most likely to select, given the fact that its choice was random, and to decide which of two possible gambles they wanted to accept (see Figure 4.1 for an example of a trial and trial timing)[1]. Participants had to decide between taking the risk of choosing the least likely outcome, putting a high number of credits at stake, or choosing the most likely outcome with only 1 credit at stake. To ensure that the youngest participants would understand this instruction, all participants were told to think of the computer as someone who picks a

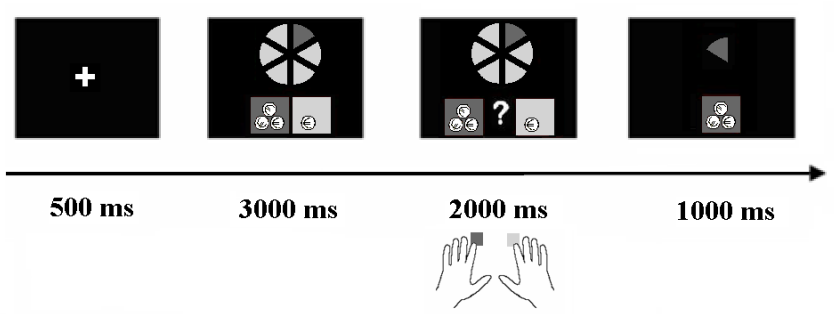

Figure 4.1 *Task example of a low-risk trial. Participants viewed the cue for 2000 ms, followed by the cue and target. Participants had 1500 milliseconds to give a response, after which gain or loss feedback was presented for 2000 ms, along with the choice of the computer. Gain was indicated by +1 and loss was indicated by -1.*

piece of cake with their eyes closed. The valence of the feedback participants received always was the consequence of the combination of the computer's random choice (according to the different proportions of the two colors) for either pink or brown and the participant's decision. If these two matched, the stake associated with the participants choice was added to the total points score, if they did not match, the stake was subtracted from the total points score. Participants were instructed to try to win as many credits as possible on every trial. To prevent participants

[1] Figure 4.1 was not included in the published manuscript, but is shown here to facilitate comparisons between the different versions of the Cake Gambling paradigm described in this thesis.

from losing motivation due to disappointment following losses, we explained that the computer's choice was random, like it would be if someone who is blindfolded chooses, and winning was associated with some luck in addition to trying your best. For this reason we also didn't stress the total points score (participants were not shown their cumulative earnings on every trial), but we told participants to try and win on as many trials as possible. However, to keep participants engaged in the task we showed the cumulative score during breaks and at the end of the task and we included a small prize in each age group for the participant with the highest number of credits in total at the end of the experiment.

4.2.3 Sensation Seeking Scale

All participants over 11 years of age completed the Zuckerman's Sensation Seeking Scale (SSS) (Zuckerman, Eysenck,& Eysenck,1978). This scale has previously been adapted for Dutch adults (Feij & Van Zuilen, 1984) and adolescents (Feij & Kuiper, 1984). Participants completed the SSS appropriate for their age. Adolescents completed the adolescent version of the SSS that consists of five sub-scales measuring Extraversion, Emotionality, Impulsivity, Thrill and Adventure Seeking aspects of Sensation Seeking (TAS), and Disinhibition and Experience Seeking aspects of Sensation Seeking (Dis/Es). Some of the Dis/Es sub-scale items concerning, for example, experience with illegal drugs or sex were considered inappropriate for the youngest participants. Therefore 11-12 year olds completed a version of the SSS that did not include this sub-scale. The TAS, and Dis/Es sub-scales were examined as a measure of sensation seeking, because these sub-scales are distinguishable in both the adult and adolescent SSS version. The TAS sub-scale consists of 11 'true/false' items, such as 'I prefer to be in a place where there is a lot going on', the Dis/Es sub-scale consists of 8 'true/false' items, such as 'I would like to experience what it is like to use illegal drugs'. The Tas and Dis/Es sub-scales have an internal consistency of .79 and .69 respectively. Adults completed the adult SSS containing TAS (12 items, internal consistency .80), Disinhibition (12 items, internal consistency .78), and Experience Seeking (14 items, internal consistency .74) sub-scales. The adult SSS consists of questions such as 'I like wild, uninhibited parties' that have to be answered using a 5-point scale (1= never, 2= rarely, 3= sometimes, 4= usually and 5= always).

4.2.4 Raven Standard Progressive Matrices

Participants filled out the Raven Standard Progressive Matrices task (Raven SPM) in order to obtain an estimate of their ability to form perceptual relations and reason by analogy. The Raven Standard Progressive Matrices (SPM) is a non-verbal test designed to measure general intellectual ability (Raven, Raven & Court, 1998). The SPM consists of 60 items, five sets (A, B, C, D, & E) of 12 items each. Each item consists of a figure from which one piece is missing. Below the figure either six (sets A & B) or eight (sets C through E) pieces are displayed that can be used to complete the figure. Only one of these is correct. The different sets and items within the sets are increasingly difficult.

4.2.5 Procedure

All participants were tested individually in a quiet laboratory or classroom. All participants completed all tasks. Stimuli were presented in color against a black background on a 15-inch computer screen placed at a distance of approximately 70 centimeters from the participant. Preceding the task participants were given verbal instructions and were shown examples of trials and feedback displays. Following this instruction, all participants performed 15 practice trials on the laptop computer. Care was taken that all participants understood the instructions after practice. The Gambling task consisted of 270 trials and took approximately 30 minutes to complete, including instructions and 3 short breaks. The total points score was shown during the three breaks and at the end of the task. The colors pink and brown corresponded to the left and right index finger, this mapping was counterbalanced between subjects to control for key preference. Color credit associations were counterbalanced within subjects to control for a possible color preference. The Raven SPM (approx. 25 minutes to complete) and the SSS (approx. 10 minutes to complete) were administered after completion of the gambling task. All participants were given the opportunity to take a short break following the gambling task, and were offered a drink and cookie. The total duration of the experiment was approximately 80 minutes, after completion of the experiment participants were thanked for participation, the participant with the most credits within each age group received a small reward.

4.3 Results

4.3.1 Cake Gambling Task Performance

Participants' performance was examined by computing the percentage of risky choices for every combination of the probability of winning and the number of credits to gamble with. Risky choices were defined as those choices for which the participants chose to gamble with the highest number of credits, even though these were associated with a small (5:1, 4:2) or equal (3:3) probability of winning. The data were submitted to repeated measures ANOVAs with Age Group (5) and Gender (2) as between-subjects factors and Probability (5:1, 4:2, 3:3) and Credits (1, 3, 5, 7, 9) as within-subjects factors. The percentages of risky choices, for all age groups separate, are presented in Figure 4.2A.

As can be seen in Figure 4.2A, when the number of credits that could be gambled with was the same for both colors (credits = 1), participants had no preference for either pink or brown in the 3:3 condition (the number of choices for each color was at chance level). In contrast, they avoided the color associated with the lowest probability of winning in the 4:2 and 5:1 conditions (main effect Probability, F (2, 166) = 363.16, $p < .001$). This effect of probability did not differ between age groups ($p = .65$) or genders ($p = .24$), showing that all participants were able to judge probabilities.

When the number of credits to gamble with increased, the percentage of risky decisions also increased (main effect Credits, F (4, 332) = 54.78, $p < .001$). Importantly, this effect was more pronounced for the conditions with the highest probability of winning, (Probability x Credit interaction: F (8, 664) = 8.09, $p < .001$). Separate ANOVAs for each of the Probability conditions confirmed that this effect was observed for all probability conditions. That is, in the 3:3 condition the 1 Credit condition resulted in chance level performance. In contrast, the 3, 5, 7 and 9 Credit conditions were associated with more risky choices, and did not differ from each other (p's > .05). Similar post-hoc ANOVAs for the 4:2 and 5:1 conditions showed an increase in risky choices associated with each increase in credits (all p's < .05). Contrary to expectations, and demonstrated in Figure 4.2A, there were no differences in the pattern of risky decision-making between the age groups (all p's > .37).

Our analyses focused on the comparison of age groups, not age as a continuous variable to facilitate the interpretation of developmental changes in behavior. In addition we submitted participants' raw ages as a covariate factor to a mixed model ANCOVA on the Cake Gambling Task data with Gender (2) as a between-subjects factor and Probability (3) and Credits (5) as within-subjects factors. Importantly, none of the effects that resulted from our initial analyses were altered by including Age as covariate; again no changes in performance with age were found.

4.3.2 Gender differences

In contrast to the absence of an age difference in risky decision-making, there were pronounced differences in the decision-making patterns of males and females. That is, the percentage of risky choices was higher for male participants compared to female participants (main effect Gender, F (1, 83) = 9.22, $p < .01$). Moreover, this difference in the percentage of risky decisions between male and female participants increased with the number of Credits at stake (Gender x Credits interaction, F (4, 332) = 3.06, $p = .05$). This interaction is displayed for the five age groups in Figure 4.2B. Male participants made 4.56%, 7.77%, 9.18%, 12.62%, and 11.45% more risky choices than females when gambling with 1, 3, 5, 7 and 9 credits respectively (all p's < .05). This pattern was found to be consistent from late childhood through early adulthood. No significant interactions with Age Group were found.

4.3.3 Performance during the task

Even though the Cake Gambling paradigm was designed to minimize the importance of learning for task performance, it is possible that participants tried to optimize their behavior by learning from the outcomes of their choices over the course of the task. To examine task performance over time, we divided the task in three blocks of 90 trials. The results from this repeated measures ANOVA with Task block (3), Probability (3), and Credits (5) as within subjects factors and Age group (5) as between subjects factor mimicked the results from the previous analyses, showing an increase in the percentage of risky decisions with an increase in the probability of winning, and the number of credits that could be gambled with for all age groups (Probability x Credits F (8, 536) = 5.79, p <.001). This pattern did not differ between task blocks

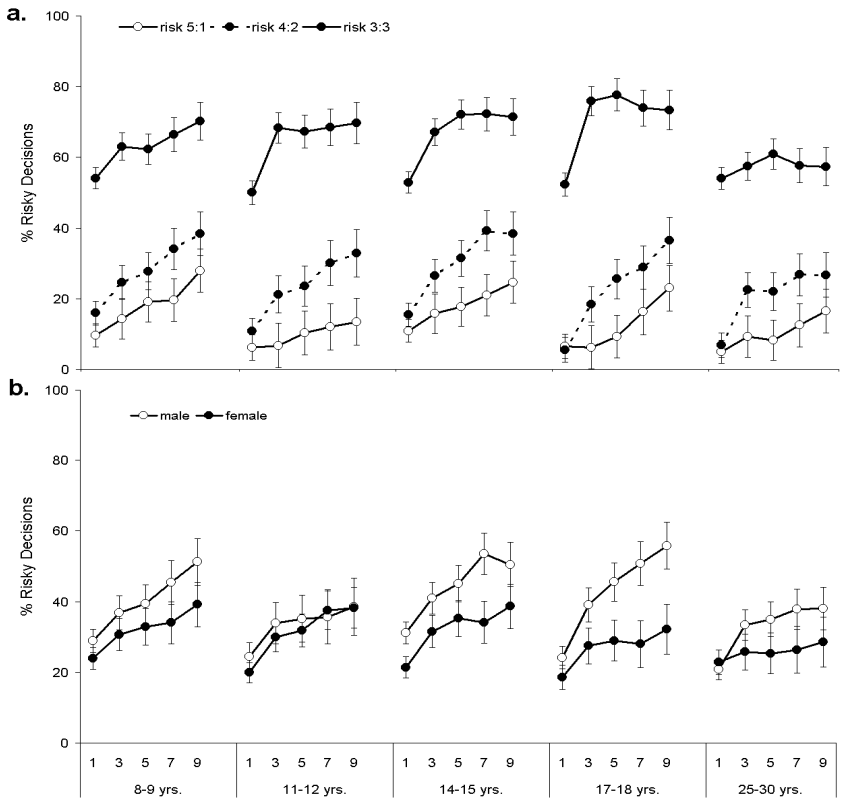

Figure 4.2 *Average percentage of risky choices plotted for all age groups as a function of the number of credits gambled with (1, 3, 5, 7 or 9) for a.) the different probabilities of winning (3:3, 4:2, 5:1), and b.) male and female participants. In all age groups gambling increases with the probability of winning and with the number of credits, and male participants made more risky decisions than female participants.*

(Probability x Credits x Task block, p >.05). A main effect of Task Block (F (2, 146) = 11.70, p <.001), indicated that participants took more risks during the first trial block than during the last two trial blocks. This main effect was qualified by a Probability x Task Block interaction (F (4, 292) = 4.61, p = .001). Separate ANOVAs for each of the probability conditions showed that the decrease in the percentage of risky decisions from the first to the later blocks of the task was most pronounced in the 4:2 condition, that is, the percentage of risky choices decreased from the first (M = 32.76, SD = 21.99) to the second block (M = 24,62, SD = 22.63) as well as from the second to the third block (M = 20.78, SD = 23,36) (p <.001). No differences in risk taking behavior over time were observed in the 3:3 condition (p > .05) (M =

66.31, SD = 18.95, M = 63.13, SD = 22.61, and M = 62.48, SD = 23.84 respectively), in the 5:1 condition the percentage of risky choices decreased from the first block (M = 18.40, SD = 17.88) to the second block (M = 15.00, SD = 21.70) ($p < .05$), but did not differ between the second block and the third block (M = 13.46, SD = 21.78) ($p > .05$) Again, there were no interactions with age group.

4.3.4 Sensation Seeking

Participants' raw scores were z-transformed and a median split, creating groups of high sensation seekers and low sensation seekers was performed for each age group, gender and Sensation Seeking sub scale separately. This technique has been shown to be unlikely to change the conclusions drawn from the results while it facilitates the interpretation of the results (Farrington & Loeber, 2000). The 11-12 year olds, 14- 15 year olds, 17-18 year olds and 25-30 year olds raw scores on the Thrill and Adventure Seeking sub scale of the Sensation Seeking questionnaire were M = 5.89, SD = 2.45; M = 6.85, SD = 2.48; M = 8.06, SD = 2.59; and M = 6.11, SD = 3.02 respectively, and 14- 15 year olds, 17-18 year olds and 25-30 year olds respective raw scores on the Disinhibition/Experience Seeking sub-scale of the sensation seeking questionnaire were; M = 2.05, SD = 1.36; M = 2.88, SD = 1.90; and M = 10.63, SD = 4.39. Interactions with the task manipulations were only significant for the Disinhibition/Experience Seeking Scale (DIS/ES). Participants labeled as high sensation seekers on the Dis/Es scale showed more risky decision-making with an increase in the probability of winning compared to participants labeled as low sensation seekers on this scale (Probability x Dis/Es interaction, F (2, 88) = 4.12, $p < .05$). This interaction was qualified by a Probability x Credits x Dis/Es interaction, F (8, 35) = 2.24, $p< .05$) showing that participants labeled as high sensation seeking took more risks when the amount of credits that could be gambled with increased compared to participants labeled as low sensation seeking.

4.3.5 *Raven SPM*

As expected, the number of correct solutions on the Raven SPM task increased with age (F (4, 76) 20.84, $p < .001$). Post hoc Tukey tests revealed that the 8-9 year olds were the least accurate (M = 37.67, SD =

8.94), followed by 11-12 year olds (M = 43.89, SD = 5.06) and 14-15 year olds (M = 44.87, SD = 4.00), who did not differ from each other. Finally, the highest scores were achieved by the 17-18 year olds (M = 51.73, SD = 3.04), and 25-30 year olds (M = 53.37., SD = 4.66), who also did not differ from each other. Raven scores were z-transformed in order to enable comparisons between the different age groups. Correlations were run to determine whether or not inductive reasoning ability may influence the findings. However, there was no correlation between z- transformed Raven SPM scores and the average percentage of risky decisions (r = -.06, p = .572). The SPM scores were then entered as a covariate in a repeated measures ANOVA with Gender (2) and Group (5) as between-subjects factor and Probability (5:1, 4:2, 3:3) and Credits (1, 3, 5, 7, 9) as within-subjects factors. This analysis showed that Raven SPM scores were no significant covariate (F (1, 70) = .112, p = .74), and including Raven SPM scores as a covariate did not change the pattern of results.

4.4 Discussion

This study examined the development of risk perception, an important aspect of decision-making, in participants aged 8-30 using the Cake Gambling Task, a child friendly gambling paradigm inspired by the Cambridge Gambling Task (Rogers et al., 1999). In particular, the focus of the study was on two aspects of risk perception: probability estimation and evaluation of reward. In concurrence with previous findings by Rogers and colleagues with a similar paradigm in adults (1999), we found that in participants from all age groups an increase in the probability of winning, and an increase in the number of credits associated with gambling, resulted in an increase in the number of risky decisions. Contrary to our expectations, we did not find differences in task performance between the age groups. Therefore, both the likelihood of winning and the magnitude of the reward associated with winning contribute to decision-making from middle childhood on, suggesting that increases in risky behavior that are observed in adolescence are not likely to be the consequence of immature risk perception abilities.

The results are in sharp contrast with the results of previous developmental studies that have used the IGT or similar tasks which

have shown age related changes in risky decision making throughout adolescence (Overman, 2004; Crone & Van der Molen, 2004). These age related changes are therefore likely to be related to task demands that are specific to the IGT. As mention in the introduction, The IGT (Bechara et al., 1994) and reversal learning tasks (Rolls et al., 1994) differ from the Cambridge Gambling Task (Rogers, 1999) and the Cake Gambling Task in that they place great demands on working memory and outcome processing in addition to risk perception abilities. In these tasks participants have to infer the task contingencies based on feedback they receive about their decisions over trials, whereas in the Cambridge Gambling Task (Rogers et al., 1999) and Cake Gambling Task all the information is presented to participants on any given trial. The current results suggest that developmental differences in decision making as measured with the IGT are associated with the demands that this task places on the ability to infer task contingencies over trials.

More support for the hypothesis that the IGT and the Cake Gambling Task tap into different processes and underlying brain circuitry comes from the comparison of gender differences. Interestingly, on the Cake Gambling Task, male participants in all age groups take *more* risks than female participants, mirroring the results of self-report studies that report males to be more risk taking in real life (Byrnes, Miller & Schafer, 1999), but contradicting prior findings using the IGT that show male participants to outperform female participants (e.g., Overman, 2004). Advantageous performance on the IGT requires participants to learn which decks are profitable, and in order to do this, outcome processing as well as updating information kept in working memory are important. The higher number of advantageous choices for men relative to woman on the IGT could be associated with aspects of contingency learning, rather than risk perception. Support for the idea that the neural correlates of IGT performance differ between men and women comes from a study by Bolla, Eldreth, Matochik & Cadet (2004). The authors report that the brain mechanisms engaged by men and women when performing the IGT differ. In men activation is lateralized to the right hemisphere, and men showed more activation in right lateral OFC than women did. In contrast, in women activation was found in both hemispheres, and women showed more activation in left DLPFC than men. These findings suggest that women differ from men in the cognitive strategies they use when performing the IGT (Bolla et al., 2004). These findings suggest that male strategies result in better

learning abilities in this specific task, together with increased risk taking compared to women.

In this study, behavior did not differ between children, adolescents and young adults, suggesting that the basic mechanisms of probability estimation and reward evaluation are already in place at age 8. What then causes adolescents to engage in more risk-taking behavior than children and adults in real life? Adolescents may be highly sensitive to environmental influences. For example, Choudhury, Blakemore & Charman (2006) recently suggested that adolescence is a period which is characterized by increased social awareness. Thus, it is possible that age related differences in risk-taking are present under the influence of social pressure. Initial evidence for this hypothesis comes from a study by Gardner & Steinberg (2005), in which risk-taking on a laboratory task greatly increased in adolescents, not children and adults, when peers were physically present. Another explanation comes from epidemiological studies which have suggested that adolescents engage in risky behaviors, despite the increase in cognitive awareness of the risks involved, because they believe the risks to be acceptable (Fromme, Katz, & Rivet, 1997; Furby & Beyth-Marom, 1992; Gerrard, Gibbons, Benthin, & Hessling, 1996; Moore & Gullone, 1996). Also, adolescent risk participation correlates positively with the number of benefits the adolescent perceives associated with making a risky decision and correlates negatively with the number of potential negative consequences that are perceived (Cohn, Macfarlane, Yanez, & Imai, 1995; Goldberg, Halpern-Felsher, & Millstein, 2002; Lavery, Siegel, Cousins, & Rubovits, 1993). Therefore, adolescents may accept some probability of negative consequences because they desire the potential positive outcomes the risks might bring about (cf. Boyer, 2006, p. 302). Along this line, recently it has been suggested that adolescents might experience risks different compared to children and adults as a consequence of the rates at which motivational and cognitive control systems in the brain mature. Relatively mature motivational circuitry biases adolescents towards risky "exciting" behavior, while relatively immature cognitive control circuitry makes it difficult for adolescents to control these impulses, which makes adolescence a period of increased vulnerability to risky behavior. For example, a recent study by Galvan et al. (2006) indicates that reward anticipation in adolescence is characterized by a hypersensitive emotion-inducing system and an

under active emotion-regulation system, even when differences in performance are absent.

Decision-making is a multi-faceted concept, the perception of risk is just one of many abilities that contribute to it. The relationship between activation in the PFC and decision making behavior is complex in a similar way. Different regions of the PFC are likely to contribute to decision making behavior, and in addition to gaining insight into the development of these different regions and the component processes of decision-making the interaction between different regions will have to be taken into account in future studies.

Future research might also address some limitations in the current study. We did not include direct measures of brain activity; functional Magnetic Resonance Imaging (fMRI) studies could provide more insight into changes with development in the relative contribution of different PFC regions, such as the OFC. In a previous fMRI study using a simplified Cake Gambling task (Van Leijenhorst, Crone, & Bunge, 2006) we found that children used different brain circuitry to reach adult decisions, in the absence of differences in behavior. The present study looked at the perception of risks in a gambling task under experimentally controlled circumstances. We assume that behavior in this situation is similar to behavior in real-life, but we have to acknowledge that there could be differences between the processes involved in performing the experimental task and real-life decision making. It should also be taken into account that limited task engagement could account in part for the lack in performance differences between the age group. The overall higher level of risky decisions in male participants could reflect differences in the way they experienced the task, possibly they were more engaged because of gender related differences in the way participants interpreted the competition element. The relation between Cake Gambling Task behavior and individual differences in sensation seeking tendency, suggests that risk perception as assessed with the Cake Gambling task does relate to real-life risky behavior, and the consistent performance in all age groups over the duration of the task suggest that participants involvement in the game did not differ throughout the experiment. Also, in the Cake Gambling Task the differences between the conditions were relatively clear. More subtle differences might be required to measure

age related differences in risk estimation abilities. For example, a study by Budhani & Blair (2005) found evidence for a relation between task performance in a response reversal task and the salience of changes in task contingencies. Children with mild OFC impairments performed worse as the changes in task contingencies were more subtle.

In conclusion, the present results indicate that risk perception is already in place at the age of 8 and does not change between ages 8-30. These results suggest that increases in real-life risky behavior in adolescence are not likely to result from a protracted development of risk perception abilities which results in immature decision-making. Gender differences are consistent across this age period, with male participants taking more risks than female participants. This study adds to current knowledge about the development of decision-making abilities in that it offers insight into the relative contribution of risk perception to decision-making from childhood until young adulthood. Insight into the development of abilities that contribute to adult decision-making is important in order to better understand potential problems adolescents face.

5.

A heart rate analysis of risky decision-making, reward sensitivity, and outcome monitoring in adolescence

The ability to evaluate risks, and monitor choices and their outcomes are important components of mature decision-making. Immature decision-making and heightened sensitivity to rewards are thought to underlie adolescent risky behavior. We tested for the development of decision-making abilities in adolescence, and measured heart rate (HR) changes to gain insight in the temporal dynamics of decision-making. Participants from three age groups (11-12-year-olds, 14-15-year-olds, and 17-18-year-olds) chose between high-risk and low-risk probabilistic gambles with varying magnitudes of reward. Risk-taking decreased with age, and HR data showed that 11-12-year-olds showed a heightened sensitivity to rewards. Age related changes in HR responses were related to the anticipation of the outcome of risky decisions, not to the evaluation of outcomes. These findings support the hypothesis that a heightened sensitivity to rewards contributes to adolescent risk-taking, and suggest that developmental changes are related to the perception of risks, not their consequences.

5.1 Introduction

The slow development of decision-making has been well documented. One of the key aspects of mature decision-making is the ability to identify and avoid immediate and long-term undesirable consequences of actions, or in other words, avoid excessive risk (Beyth-Marom, 1993; Garon & Moore, 2004). Many studies have shown that children's decisions are more likely to be risky and oriented towards short-term rewards compared to adults' decisions (Blakemore & Choudhury, 2006; Boyer, 2006; Crone, Bullens, Van der Plas, Kijkuit & Zelazo, 2008; Lejuez, Aklin, Zvolensky & Pedulla, 2003; Reyna & Ellis, 1994), and that the ability to take the long term consequences of choices into account improves until late adolescence (Hooper, Luciana, Conklin & Yarger, 2004; Overman et al., 2004). Adolescence is a developmental phase in which many problems are related to risky behavior, for example involvement in accidents, experimentation with illicit drugs or alcohol, and problems in school. Immature decision-making abilities are thought to underlie these problems (Arnett, 1992; Rivers, Reyna & Mills, 2008; Steinberg, 2004).

The study of decision-making development and its contribution to risk-taking is complicated because age differences in risk-taking have been difficult to measure using laboratory tasks (see Boyer 2006 for a review). The results of previous studies using laboratory tasks of risk-taking seem inconsistent with the idea that decision-making abilities are immature in adolescence. For example, when the demands on learning and working memory are minimized by making outcome values and associated probabilities explicit, no age differences in decision-making behavior are found from age 8 to 30 (van Leijenhorst, Westenberg & Crone, 2008). Other developmental studies have shown that 5-6 year old children show an understanding of probabilities (Acredolo, O'Connor, Banks & Horobin, 1989; Schlottmann, 2001). However, in real life situations, decisions and their outcomes have to be monitored and this information has to be used to optimize behavior. The Iowa Gambling Task (IGT) was designed to mimic these real life requirements (Bechara, Damasio, Damasio & Anderson, 1994), in this task participants have to learn form the outcomes of their decisions which choice options are risky. Developmental studies using this paradigm have shown an increased ability to learn to avoid the risky options throughout adolescence (Crone & Van der Molen, 2004; Hooper et al., 2004). Importantly, these behavioral studies have limited ability

to inform us whether developmental changes in performance monitoring occur around the moment decisions are made, when the outcomes of decisions are processed, or during both these moments. Therefore, it remains unclear what aspects of child and adolescent decision-making contribute to risky behavior.

Psychophysiological measures can give further insight into the development of performance monitoring. Event-related potentials (ERPs) have been used to examine the temporal dynamics of central nervous system processes related to evaluating the outcomes of risky decisions. Gehring & Willoughby (2002) showed that negative outcomes of 2-choice gambles result in a frontally located negative brain potential, which peaks approximately 265 ms after the presentation of the negative outcome. They concluded that this ERP response, referred to as the Medial Frontal Negativity (MFN), was specific for negative outcomes, because it was not affected by information which signaled that participants had chosen the wrong gamble (i.e., when the alternative choice would have resulted in even a greater loss). This MFN potential has the same temporal dynamics as the feedback-related negativity (FRN), a brain potential which is elicited by feedback indicating an incorrect responses (Holroyd & Coles, 2002). The FRN is also associated with response uncertainty or response conflict and with the detection of errors. Localization studies examining the underlying neuroanatomical source of these negative brain potentials have reported that the resolution of negative or erroneous outcomes is located in or near the anterior cingulate cortex (ACC) (Miltner et al., 2003; Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004). Studies on the development of error-related ERP responses related to performance monitoring, suggest that error-related ERP responses continue to develop well into adolescence (Davies, Segalowitz & Gavin, 2004a, 2004b; Ladouceur, Dahl & Carter, 2004). Even though these developmental studies focused on response-related error monitoring (internal evaluation) and not on feedback-related error monitoring (external evaluation), the results lead to the hypothesis that performance monitoring is still immature in adolescents.

Performance monitoring is also reflected in autonomic nervous system changes. It is well documented that beat-to-beat heart rate changes are related to information processing demands. Heart rate decelerates when attention has to be directed to detect information relevant to the task that is performed, and accelerates when that information is processed or

used actively in working memory (Lacey & Lacey, 1974; Van der Molen, Somsen & Orlebeke, 1985). These cardiac changes are thought to result from a parasympathetic system which affects the heart very quickly resulting in a change in heart rate within tens of milliseconds (Somsen, Jennings & Van der Molen, 2004), and which is related to self regulatory cognitive functions (Posner & Rothbart, 1998). Heart rate typically slows in anticipation of a stimulus or a behavioral response, followed by an acceleratory recovery to baseline (Jennings & Van der Molen, 2002). Processing of negative performance feedback typically results in a delay of this return to baseline, as reflected in a lengthening of the inter beat interval, or heart rate deceleration (Somsen, Van der Molen, Jennings & Van Beek, 2000; Van der Veen, Van der Molen, Crone & Jennings, 2004). This lengthening suggests that heart rate is sensitive to the valence (negative/positive) of performance feedback (Somsen et al., 2000; Van der Veen et al., 2004). Similarly, the anticipation of performance feedback results in cardiac slowing, and this slowing is prolonged when outcomes are different (better or worse) than expected (Crone, Bunge, de Klerk & Van der Molen, 2005a; Crone, Bunge, Latenstein & Van der Molen, 2005b; Crone, Somsen, Van Beek & Van Der Molen, 2004b). This study suggests that heart rate changes not only respond to the valence of the feedback, but reflects a performance monitoring system that responds differentially to feedback that is informative for optimizing task performance (Crone et al., 2003; Somsen et al., 2000).

In a gambling context, we have shown that the amount of rewards associated with decisions affects the pattern of cardiac changes (Crone et al., 2005a). In this study, young adult participants gambled for low or high amounts of money and we studied the cardiac changes during the anticipation and evaluation of the outcomes of these gambles. As expected, we observed heart rate slowing during periods when participants were anticipating the outcomes of gambles, and this slowing was larger when more money was at stake. Further, heart rate slowed more following feedback for high reward gambles relative to low reward gambles, independent of whether the feedback indicated a loss or a gain. These results show that beat to beat heart rate changes are a sensitive index of both the anticipation of the outcomes of uncertain decisions and of the monitoring of these outcomes (Crone & Van der Molen, 2007), and the high temporal resolution enables the differentiation of these response related and feedback related cognitive processes.

In prior work, we have shown that heart rate changes can be used in children and adolescents (Crone & Van der Molen, 2007; Van Leijenhorst, Crone & Van der Molen, 2007). In a study using the IGT paradigm, heart rate responses in children of three age groups (8-10, 12-14, 16-18 years old) were assessed when they were anticipating and evaluating the outcomes of choices (Crone & Van der Molen, 2007). Participants were instructed to make choices from four locations on a computer screen, and each location was associated with a high or a low reward. Over the course of the task, participants had to learn that those locations which resulted in high reward also resulted in high punishments, leading to long-term loss. In contrast, those locations which resulted in low reward also resulted in low punishment, leading to long-term gain. The feedback results were the same as previously reported in adults (Bechara, Tranel, Damasio & Damasio, 1996; Crone et al., 2004b). That is, losses resulted in larger cardiac slowing than gain, and the slowing was larger when the loss was greater or when the loss was unexpected (Somsen et al., 2000). These results show an age related difference in the ability to anticipate negative outcomes. Whereas 16-18-year-olds, comparable to adults showed differentiated autonomic responses prior to risky outcomes, the younger age groups showed autonomic responses prior to all outcomes. These results suggest that while the processing of outcomes is similar for all age groups, the anticipation of these outcomes is immature in adolescence. It should be noted that the learning requirements of the IGT put demands on working memory capacity (Bechara, Damasio, Tranel & Anderson, 1998), and it is therefore unclear whether the observed differences were related to anticipating the outcomes of risky decisions and the way in which risks are perceived, or to differences in working memory capacity and the ability to learn from the outcomes of choices.

The goal of the present study was to gain insight into adolescent risk-taking by examining the development of decision-making. Specifically, we used measures of heart rate changes to differentiate the relative contributions of the development of processes related to the anticipation and evaluation of gamble outcomes. Three age groups participated in the present study (11-12, 14-15, 17-18-years old), reflecting different stages of adolescent development (Steinberg, 2005; Westenberg, Hauser & Cohn, 2004). All participants performed a modified version of the Cake Gambling Task (van Leijenhorst et al., 2008) optimized for use in combination with autonomic measures. Participants were asked to repeatedly choose between a low-risk and a high-risk gamble, and were

instructed to try and win as many credits as possible over the course of the experiment. Stimuli were cakes composed of six wedges in two colors, pink (strawberry flavor) and brown (chocolate flavor) according to a 1:5, 2:4 or 3:3 probability distribution. As a consequence, choosing the high-risk gamble was associated with a 17%, 33%, or 50% chance of winning. We manipulated the number of credits that was associated with the different decisions; in such a way that 3 or 7 credits were associated with the high-risk gamble, and 1 credit was always associated with the alternative low-risk gamble. We expected the behavioral results to resemble those found in our previous study using this paradigm (van Leijenhorst et al., 2008), in that the percentage of choices for the high-risk gamble would increase with the probability that this choice results in a win, and with the number of credits that were associated with it.

We focused our analyses of the psychophysiological changes on the comparison of low-risk versus high-risk gambles, associated with a low or high number of credits, based on research described above that suggests that the ability to estimate probabilities matures well before adolescence. First, we examined whether cardiac changes related to outcome anticipation following high-risk gambles would differ from low-risk gambles, and whether high-risk gambles for high reward would differ from high-risk gambles for low reward. Based on prior work, we expected that cardiac slowing associated with outcome anticipation would be larger for high-risk compared to low-risk gambles, and larger for high reward than low reward gambles (Crone et al., 2005a). Prior studies have demonstrated that the psychophysiological response in anticipation of uncertain outcomes becomes more differentiated with age during adolescence (Crone & Van der Molen, 2007), in the present study we therefore examine differences in anticipatory autonomic responses in distinct phases of adolescence, using a task with minimal working memory and learning demands.

Second, we examined cardiac changes in response to the resolution of high-risk and low-risk gambles. We expected cardiac slowing in response to the outcomes of trials (Crone et al., 2003; Hajcak, McDonald & Simons, 2003; Van der Veen et al., 2004), and we expected this slowing to be larger when the outcome was unexpected (Crone et al., 2003). The current study allowed us to test whether heart rate responsiveness in adolescence is sensitive to the valence of the feedback (van der Veen et al., 2004) or to the informative value

provided by the feedback, for example when the feedback violates expectations (Somsen et al., 2000). Under the hypothesis that heart rate changes reflect the informative value of feedback, cardiac slowing was expected to be larger when high-risk gambles resulted in gain, and when low-risk gambles resulted in loss. Previous work showed that cardiac changes in response to the outcome of gambles did not show age related change (Crone & Van der Molen, 2007). Based on these findings, we did not expect age related differences in autonomic nervous system responses to loss and gain outcomes in the present study.

5.2 Method

5.2.1 Participants

Fifty adolescents distributed among three age groups participated in the experiment. Data from 7 participants had to be excluded from the analyses as a consequence of technical difficulties. Data from sixteen 11-12-year-olds (Mean = 12.22, *SD* = .55, 8 girls), sixteen 14-15-year-olds (Mean = 15.09, *SD* = .45, 7 girls), and eleven 17-18-year-olds (Mean = 18.07, *SD* = .53, 4 girls) were included in the final sample. All participants were recruited by contacting local schools in the Leiden area (the Netherlands), and selected with the help of their teachers. Written informed consent was obtained from all participants aged 18 and older. For participants younger than 18, written informed consent was obtained from a primary caregiver. In addition all participants gave verbal assent prior to inclusion in the study. Participants with learning or behavioral disorders or a history of neurological impairments, as indicated by their parents or teacher were not selected to take part in the study. No detailed information regarding parental income, parental education level, or family size of the participants was obtained. However, participants were mostly Caucasian, and came from families with average or above average SES. All procedures were approved by the Leiden University Department of Psychology Internal Review Board.

All participants completed the Raven Standard Progressive Matrices task (Raven SPM) in order to provide an estimate of participants' general intellectual ability (Raven, Raven & Court, 1998). A one-way analysis of variance (ANOVA) performed on the estimated IQ scores revealed a significant difference between the three age groups ($F(2, 41) = 5.03$, $p = .01$). Post hoc Tukey tests showed that 11-12-year-olds'

scores (Mean IQ = 119.19, *SD* = 6.57) were significantly higher than 14-15-year-olds' scores (Mean = 108.73, *SD* = 11.87). Both age groups did not differ statistically from 17-18-year-olds' average scores (Mean IQ = 112.00, *SD* = 8.94). Importantly, estimated IQ scores for all age groups fell within the average to high average range. To test whether IQ differences influenced gambling behavior we correlated estimated IQ scores and the average percentage of risky decisions, and did not find a significant correlation ($r = .007$, $p = .97$), in addition after we excluded 5 participants (4 middle adolescents, and 1 older adolescent) with estimated IQ scores below 100, IQ scores no longer differed between age groups (Mean IQ scores were 119.19 (*SD* = 6.57), 114.00 (*SD* = 7.29), and 113.40 (*SD* = 8.06) for 11-12, 14-15, and 17-18-year-olds respectively) ($p > .05$). None of the results were affected by exclusion of these participants. Together these findings convince us that IQ as measured with the Raven SPM is not a factor in the reported effects.

5.2.2 Cake Gambling Task

In the Cake Gambling Task participants repeatedly choose between two gambles which are presented visually in order to make the choice options understandable to children. On every trial a stimulus depicting a cake composed of six wedges was presented at the center of the screen. The wedges could be brown or pink, and participants were told that these colors represented chocolate (brown) or strawberry (pink) flavored pieces of cake. The proportion of pink:brown wedges was varied systematically across trials to be 1:5, 2:4, or 3:3. In addition to varying this proportion, both colors were associated with a number of credits that formed the stake in the gambles. For each cake, one of the colors was associated with 1 credit, and the other color was associated with 3 or 7 credits. For the 1:5 and 2:4 cakes, 3 or 7 credits were always associated with the minority color, for the 3:3 cakes the 3 or 7 credits could be associated with both colors. A brown and pink square containing a number of coins, indicating the number of credits that was associated with each flavor, and a question mark were presented below each cake. On each trial the computer randomly selected one of the wedges, which resulted in a 17% (for 1:5 cakes), 33% (for 2:4 cakes) and 50% (for 3:3 cakes) chance of the color associated with the higher number of credits to be chosen by the computer. To ensure that the youngest participants would understand this instruction, all participants were told to think of the computer as someone who picks a piece of cake with their eyes closed.

Each trial started with a 500 ms fixation cross, followed by the presentation of a cake stimulus (see Figure 5.1). At this point, participants were instructed to decide and indicate with a button press which of the two possible gambles they wanted to accept. A low-risk gamble was a gamble in which one credit was at stake (which could be won or lost dependent on the outcome) whereas a high-risk gamble was

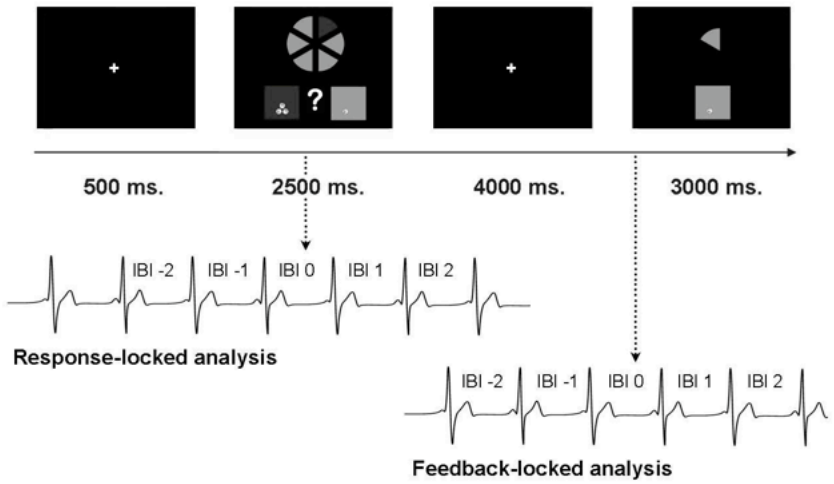

Figure 5.1 *Example of a trial in the Cake Gambling Task showing the 1:5 probability condition. Choosing the high-risk gamble (the least probable option - darker color) results in a 3 credit stake, whereas choosing the low-risk gamble (the most probable option – lighter color) results in a 1 credit stake. In this example the most likely option was chosen and 1 credit was won. Participants were given 2 Euro to play with at the beginning of the experiment. Trial timing and associated Inter beat intervals are shown. See text for further details. For the response locked analysis the average IBI length of IBI -2 was 772.01 ms (SE = 16.13); for the feedback locked analysis this was 763.94 ms (SE = 15.53).*

a gamble in which 3 or 7 credits were at stake (which could be won or lost). In the 1:5 and 2:4 conditions, low-risk gambles had a higher chance of resulting in a win, whereas high-risk gambles had a lower chance of resulting in a win. In the 3:3 conditions, the probabilities for high-risk and low-risk gambles were the same, and only the amount of credits at stake differed. The stimulus remained on the screen for 2500 ms and participants had to make their response within this time period with the index and middle finger of their dominant hand. The stimulus and response were followed by a 4000 ms period during which a fixation cross was presented and participants anticipated the outcome of the gamble that they had chosen. This time allowed for analysis of heart rate and skin conductance changes related to the decision and outcome

anticipation phase of the trial. Following this fixation period a feedback stimulus was presented for 3000 ms. The valence of the feedback participants received was the result of the combination of the computer's random choice for either pink or brown and the participant's decision for the gamble associated with either pink or brown. If these two matched, participants received feedback indicating that they won the credits associated with the gamble they had chosen, and these credits were added to the total points score. If they did not match, participants received feedback indicating that they lost the credits associated with the gamble they had chosen and these credits were subtracted from the total points score. Participants were instructed to try to win as many credits as possible on every trial.

5.2.3 Psychophysiological Measures.

During performance of the Cake Gambling Task, participants' electrocardiogram (ECG), skin conductance levels (SCL) and respiration were continuously recorded using a Biopac MP150 system. The ECG was recorded from three electrodes, attached via the modified lead-2 placement. SCL was recorded using a constant voltage (0.5 V) with two electrodes attached to the middle and index fingers of participants' non dominant hand. Respiration was recorded using a temperature sensor placed under the nose. ECG signals, SCL and respiration signals were sampled and recorded at a rate of 400 Hz. Inter Beat Intervals (IBIs) were computed based on the ECG signals and were visually screened for physiologically impossible readings and artifacts, IBI scores which were more than 2 SD removed from the mean were taken out of the analysis using an algorithm developed in our laboratory. It should be noted that a lengthening of the IBI, or a larger IBI value indicates a slowing of heart rate. The results of the skin conductance and respiration measures are not presented in this report.

5.2.4 Procedure

All participants were tested individually in a quiet room. Stimuli were presented in color against a black background on a 17-inch laptop computer screen placed at a distance of approximately 70 centimeters from the participant. Preceding the task participants were given verbal instructions and were shown examples of trials and feedback displays. Following this instruction, all participants performed 21 practice trials

on the laptop computer. Care was taken that all participants understood the instructions after practice.

At the start of the task all participants were given 2 Euro to gamble with; they were told that dependent on the number of credits they would win over the course of the task, they could lose, win or double the 2 Euro. The Cake Gambling Task consisted of 168 trials presented in four blocks of 42 trials and took approximately 40 minutes to complete, including instructions and 3 short breaks. The total points score was shown during the three breaks and at the end of the task. The colors pink and brown corresponded to the index and middle fingers of participants' dominant hand. This mapping was counterbalanced between participants to control for possible key preference, and color-credit associations were counterbalanced within subjects to control for a possible color preference. The Raven SPM (approx. 25 minutes to complete) was administered in the classroom within two weeks following the experimental task. After completion of the experiment participants were thanked for participation, and all were paid 4 Euro.

5.3 Results

The results are described in 2 sections; the first section describes the behavioral results, the second section describes the heart rate results. To correct for non-equal variances in the analyses with heart rate as within-subject factors, degrees of freedom were adjusted using the Huynh–Feldt correction.

5.3.1 Cake Gambling Task performance: Risk-taking

Participants' performance was examined by computing the percentage of choices for high-risk gambles for every combination of the probability of winning and the amount of credits. In addition, mean reaction times were recorded. Choices for high-risk gambles were defined as those trials for which participants chose the 3 or 7 credits gamble over the 1 credit alternative, even though this choice was associated with a smaller (1:5, 2:4) or equal (3:3) probability of resulting in a win. Choice data were submitted to repeated measures ANOVAs with Age Group (11-12-year-olds vs. 14-15-year-olds vs. 17-18-year-olds) as between-subjects factors and Probability (1:5 vs. 2:4 vs. 3:3) and Credits (3 or 7) as within-subjects factors. This analysis

resulted in main effects of Credits ($F(1, 40) = 26.11$, $p < .001$), Probability ($F(2, 80) = 20.65$, $p < .001$), and a Probability x Credits interaction ($F(2, 80) = 9.47$, $p < .001$); participants were willing to choose the high-risk gamble more often when 7 credits could be won (Mean = 52.75 %, SE = 2.71) compared to when 3 credits could be won (Mean = 33.67 %, SE = 3.46), and more often when the probability of winning was 2:4 (Mean = 46.67 %, SE = 2.29) or 3:3 (Mean = 48.31%, *SE* = 2.60) relative to when it was 1:5 (Mean = 34.66 %, SE = 3.45). The latter effect was amplified in the 7 credits condition relative to the 3 credits condition. No main effect of Age Group ($p = .08$) or interaction of Age Group with any of the effects reported above was found (all p's > .1), this suggested that risk-taking behavior did not differ between early, middle and late adolescents (see Figure 5.2). However, when age as a continuous variable was correlated with average risk-taking, a negative correlation was found, suggesting less risk-taking in older adolescents. ($r = -.36$, $p = .02$). Correlation analyses for each credit condition separately showed that this correlation was only significant in the 3-credit condition ($r = -.33$, $p < .05$), not in the 7-credit condition. Together, these results show that younger participants were more willing to choose the high-risk gamble when 3 credits could be gained compared to older participants.

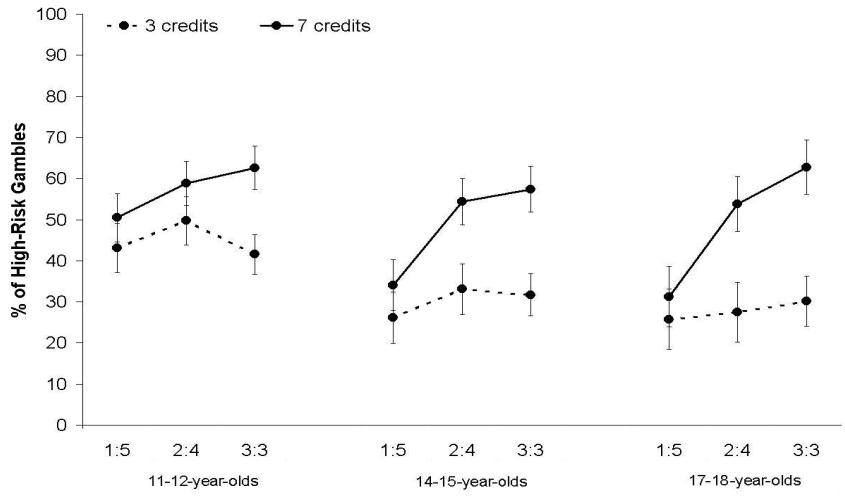

Figure 5.2 *Average percentage of choices for high-risk gambles plotted for 11-12, 14-15 and 17-18-year-olds as a function of the number of credits at stake (3 or 7) for the different probabilities of winning (1:5, 2:4 or 3:3). Error bars represent standard errors*

5.3.2 Reaction Times

Reaction time (RT) data for high-risk and low-risk gambles were submitted to repeated measures ANOVAs with Age Group (3) as between-subjects factors and Probability (1:5, 2:4 or 3:3), Credits (3 or 7), and Choice type (high-risk or low-risk) as within-subjects factors. This analysis resulted in a main effect of Choice type $F(1, 40) = 5.80$, $p < .05$. Choices for high-risk gambles were made faster (Mean RT = 1241.50, SE = 33.15) compared to choices for low-risk gambles (Mean RT = 1302.57, SE = 33.31). There were no other main or interaction effects. Mean RTs for 11-12 year olds (Mean = 1245.03, *SE* = 49.58), 14-15 year olds (Mean = 1306.07, *SE* = 49.58) and 17-18 year olds (Mean = 1265.02, *SE* = 59.79) did not differ ($p = .68$), and the effect of type of choice on RTs did not differ between the age groups ($p = .53$) (RTs per reward condition are reported in Table 5.1).

Table 5.1 *Mean reaction times for 11-12, 14-15, and 17-18 year olds for high-risk (3 or 7 credits) and associated low-risk (1 credit) choices.*

		High-Risk gamble		**Low-Risk gamble**	
		Mean RT	*SE*	*Mean RT*	*SE*
11-12 yrs.	*3 credits*	1241.45	64.06	1279.03	52.96
	7 credits	1188.67	62.61	1270.96	58.43
14-15 yrs.	*3 credits*	1247.77	64.06	1317.32	52.96
	7 credits	1339.04	62.61	1320.13	58.43
17-18 yrs.	*3 credits*	1226.24	77.26	1317.13	63.88
	7 credits	1310.84	75.52	1310.84	70.47

Taken together, consistent with previous reports, participants chose high-risk gambles more often when the probability of winning and the number of credits at stake were higher. Choices for high-risk gambles were made faster than choices for low-risk gambles, suggesting that either the latter required more deliberation time or that the high-risk gambles were selected more impulsively. Consistent with previous studies, differences in performance between the adolescent age groups were small. There were no age differences in performance when a large reward could be won, but when a small reward was associated with the high-risk decision, younger participants were more willing to take the risk and gamble for this reward. In the next section we examine in what way beat to beat changes in heart rate are related to risk-taking behavior

and whether there are developmental differences in the sensitivity of this measures to specific phases of the task.

5.3.3 Risk-taking as reflected in Heart rate changes

The results from the analysis of changes in inter-beat-intervals (IBI) are organized in two sections, associated with two distinct phases of decision-making trials. The first phase involves the response and the anticipation of the outcome of gambles. The second phase involves the processing of these outcomes and their evaluation. In the analysis of both phases, we focused on whether the participant chose a low-risk or high-risk gamble, and whether the high-risk gamble option was associated with 3 or 7 credits. The current design and number of observations did not allow us to also distinguish between probability conditions and with reward amounts in one analysis. In addition, analyses on heart rate changes for the different probability conditions informed us that including probability in the analyses did not add to the interpretation of the mechanism underlying developmental changes in decision-making[1]. Therefore all analyses presented below are conducted on values collapsed across probability conditions.

5.3.4 Heart rate changes associated with decision-making and outcome anticipation.

To examine cardiac responses related to participants' choices, seven inter beat intervals (IBIs) were selected around the response, IBIs were computed for high-risk and low-risk gambles separately for the conditions in which 7 or 3 credits were at stake. The IBI concurrent to the response is referred to as IBI 0, and all IBIs were referenced to IBI -2 (which functioned as a baseline) (see Figure 5.1 for a schematic example of cardiac timing relative to trial timing). A larger IBI value

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[1] IBIs were computed for high-risk and low-risk gambles for the 1:5, 2:4 and 3:3 Probability conditions separately. A Probability (1:5 vs. 2:4 vs. 3:3) x Choice type (high-risk vs. low-risk) x IBI (1, 2, 3) x Age group (11-12-year-olds, 14-15-year-olds, 17-18-year-olds) repeated measures ANOVA resulted in a main effect of IBI F (2, 80) = 28.03 $p < .001$; heart rate slowed in anticipation of the response (from IBI -2 to IBI 0), followed by an acceleratory recovery to baseline (IBI 1, 2, 3 and 4). The Probability x IBI and the Probability x Choice type x IBI interactions did not reach significance (p's > .5). No differences between the age groups were found for any of these effects (all p's > .2), suggesting that the cardiac changes related to decision-making associated with the different probabilities did not differ between age groups.

indicates a slowing of heart rate relative to this baseline. To show the temporal characteristics of the cardiac changes associated with the response and anticipation of the outcome of gambles, the values of IBI -1, 0, 1, 2, 3, and 4 relative to the value of IBI -2 are plotted in Figure 5.3 for each of the Choice and Credit condition for the different age groups. These plots show the cardiac changes that are typically observed when participants prepare for a significant event; heart rate slows (an increase in IBI length) preceding the response, and subsequently returns to baseline (acceleratory recovery). A preliminary analysis of IBI -2 (Mean length = 772.01 ms, *SE* = 16.13 ms) revealed no significant differences in IBI length between the Age groups (p = . 28), confirming that this IBI can be validly used as a baseline when comparing task related heart rate changes between the different age groups. Given that there was a 500 ms inter trial interval and the average response times were around 1200 ms, the IBI -2 value for the response locked analysis does not overlap with heart rate changes following feedback on the previous trial (see Figure 5.1).

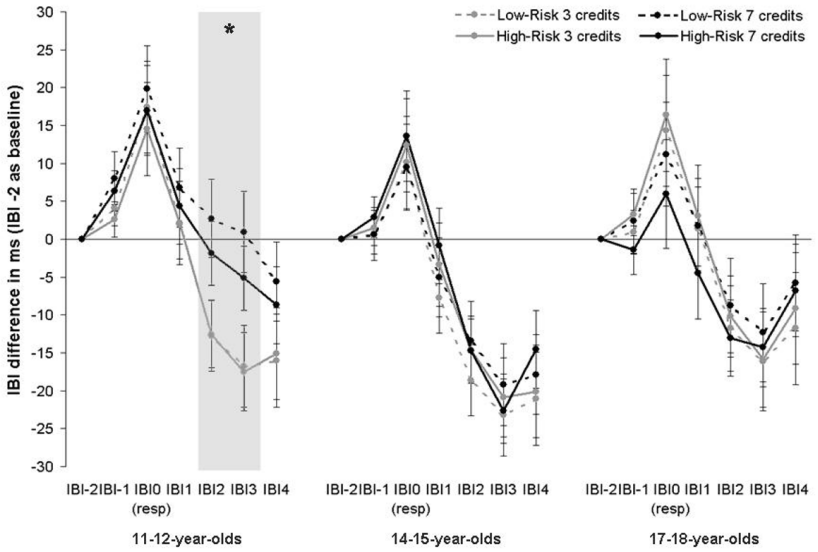

Figure 5.3 Heart rate changes related to high-risk (3 or 7 credits) gambles and associated outcome anticipation plotted for 11-12-year-olds, 14-15-year-olds and 17-18-year-olds. (denotes significant effect at p <.05). Error bars represent standard errors.*

To examine cardiac changes related to participants' choices and the anticipation of outcomes related to those choices, we focus the analysis on the first three IBIs following the response (IBI 1, 2 and 3). IBIs

immediately following responses (Somsen, Van der Molen, Jennings & Orlebeke, 1985; Somsen et al., 2000) and feedback presentation (Crone, Somsen, Zanolie & Van der Molen, 2006; Crone et al., 2003) have been found to be most sensitive to HR changes. In addition, the feedback is not presented until after IBI 4, therefore cardiac changes in these IBIs cannot reflect outcome processing. This data selection resulted in a Credits (3 vs. 7) x Choice type (high-risk vs. low-risk) x IBI (1, 2, 3) x Age group (11-12-year-olds, 14-15-year-olds, 17-18-year-olds) repeated measures ANOVA. This ANOVA resulted in a main effect of IBI F (2, 80) = 29.53 $p < .001$, and a Credits x IBI interaction F (2, 80) = 4.25, $p < .05$, which showed that the heart rate responses differed for 3 credit and 7 credit gambles. An interaction with Age group (Age group x Credits x IBI, F (4, 80) = 4.19, $p < .005$), demonstrated that this heart rate pattern was influenced by the Credit condition to a different extent in the different age groups. ANOVAs for the age groups separately showed that for the 14-15-year-olds, and 17-18 year olds heart rate changes related to the response and associated outcome anticipation phase were not significantly influenced by the amount of credits at stake (p's $> .05$). In contrast, for the 11-12 year olds, the acceleratory recovery to baseline following the response was delayed for 7 credit gambles compared to 3 credit gambles (Credits x IBI, F (2, 30) = 6.55, $p = .01$). Follow up ANOVAs showed that the difference between gambles or 3 and 7 credits for 11-12 year olds was not significant at IBI 1 ($p = .52$), but was significant at IBI 2 F (1, 15) = 4.93, $p < .05$, and IBI 3 F (1, 15) = 5.90, $p < .05$. Interestingly, this effect was not modulated by whether 11-12-year-olds chose a low-risk or a high-risk gamble (Credits x Choice, $p = .16$; Credits x Choice x IBI, $p = .79$); the IBI response during outcome anticipation for the 7 credits relative to 3 credits condition was similarly elevated for both low-risk *and* high-risk gambles.

In sum, even though in all age groups heart rate changes did not differ for high-risk and low-risk choices, there were age related differences in heart rate responses during the outcome anticipation phase. In particular, 11-12 year-olds' heart rate decelerated in anticipation of the outcome of 7 credit gambles compared to 3 credit gambles, independent of whether they had chosen a high-risk or low-risk gamble. In contrast, no differences between conditions were found for the 14-15 and 17-18 year olds. These results suggest increased performance monitoring associated with the anticipation of the outcomes of high reward gambles in early adolescence.

5.3.5 Cardiac changes associated with outcome processing

To examine cardiac responses related to the processing of the outcomes of gambles, seven IBIs were selected around the presentation of the feedback, IBIs were computed for loss and gain trials, following 7 credits high-risk gambles, 3 credits high-risk gambles, and 1 credit low-risk gambles separately. For this analysis the IBI concurrent to the presentation of the feedback is referred to as IBI 0, and all IBIs were referenced to IBI -2 (the second IBI preceding the presentation of the feedback) (see Figure 5.1). Again, to show the temporal characteristics of cardiac changes , the values of IBI -1, 0, 1, 2, 3, and 4 relative to IBI -2, are plotted in Figure 5.4 following gain and loss feedback associated with 1 credit low-risk gambles and 3 or 7 credit high-risk gambles separately. Figure 5.4 shows the expected pattern; heart rate slows in anticipation of the presentation of the feedback, and subsequently returns to baseline. A preliminary analysis of IBI -2 (Mean length = 763.94 ms, *SE* = 15.53 ms) revealed no significant differences in IBI length between the Age groups (p = .32), confirming that this IBI could be validly used as a baseline when comparing task related heart rate changes between the different age groups. Similar to the response locked analysis, the IBI -2 value for the response feedback locked analysis does not overlap with heart rate changes following the preceding response (see Figure 5.1).

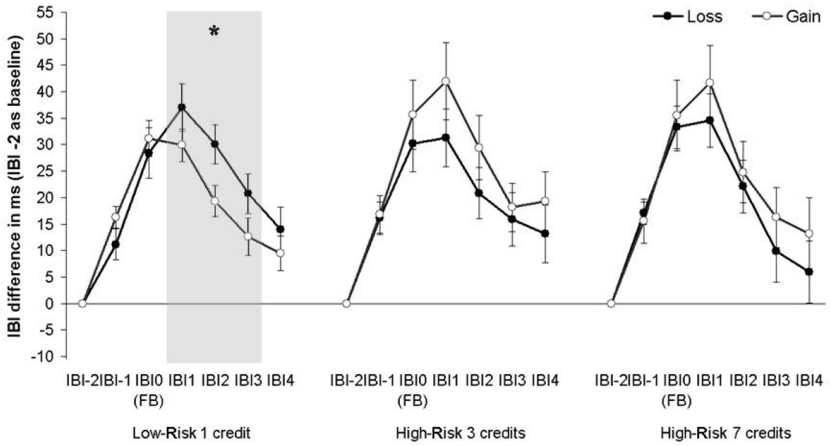

Figure 5.4 *Heart rate responses related to loss and gain feedback for high-risk (3 or 7 credits) and low-risk (1 credit) gambles. (* denotes significant effect at $p < .05$). Error bars represent standard errors.*

To examine cardiac changes related to the processing of gain and loss outcomes, we focused the analysis on the first three IBIs following the presentation of the feedback (IBI 1, 2 and 3). The feedback remains visible for 3000 ms, therefore cardiac changes in these IBIs are unlikely to reflect anticipation of the next trial. This data selection resulted in a Credits (1, 3, 7) x Feedback (gain vs. loss) x IBI (1, 2, 3) x Age group (11-12-year-olds, 14-15-year-olds, 17-18-year-olds) repeated-measures ANOVA.

The ANOVA resulted in a main effect of IBI, F (2, 80) = 27.30, p < .001, and a Credits x Feedback interaction F (2, 80) = 3.17, p < .05. No differences between the Age groups were found (all p's > .16), showing that in contrast to the decision phase, cardiac changes related to the outcome of gambles were similar in early, middle, and late adolescence. As can be seen in Figure 5.4, heart rate slowing following the presentation of the feedback was larger for gain relative to loss outcomes of high-risk gambles (3 and 7 credits), whereas heart rate slowing was larger for loss relative to gain outcomes for low-risk gambles (1 credit). These observations were statistically verified with ANOVAs for the credit conditions separately, which showed that the difference in the cardiac response following gain and loss feedback was not significant for 3 credit (p = .21) and 7 credit (p = .28) outcomes, but for low-risk 1 credit outcomes heart rate slowed more following feedback indicating loss (M = 29.29, SE = 3.48) relative to feedback indicating gain (M = 20.62, SE = 2.87) (main effect feedback; F(1, 40) = 6.22, p = .017)

In summary, the analysis of autonomic nervous system responses to the outcome of gambles indicate that heart rate slowed following the presentation of the feedback, and that this slowing was larger for loss than for gain feedback following low-risk gambles, whereas following high-risk gambles heart rate changes did not differ significantly for gain and loss. These results show that heart rate is not simply sensitive to the magnitude of gain or loss, but is responsive to the informative value of the feedback. That is, the heart rate response is more pronounced when the outcome is associated with the least predictable outcome (loss following a low-risk gamble). Consistent with prior studies, there were no age differences in the effects of feedback on autonomic nervous system changes (see also Crone & Van der Molen, 2007).

5.4 Discussion

The goal of this study was to gain insight into adolescent risk-taking. We examined adolescents' decision-making in a gambling task, and measured associated beat to beat changes in heart rate. This technique enabled us to differentiate the developmental trajectories of cognitive processes related to the anticipation and evaluation of the outcomes of gambles separately. The paradigm also allowed us to gain insight into age related changes in performance monitoring and the sensitivity to rewards in adolescence.

In a previous behavioral experiment in which we used a paradigm similar to the paradigm used here, we showed that participants ranging in age from 8 to 30 years take both the probability of winning and the number of credits associated with a gamble into account when they make risky decisions (van Leijenhorst et al., 2008). Our behavioral results are consistent with this finding; the percentage of choices for high-risk gambles increased with the associated probability of winning, and was higher for high reward gambles than low reward gambles. Gambling behavior did not differ between the age groups for high reward gambles, however, when a small reward was at stake younger adolescents were more likely to choose a high-risk gamble than older adolescents. This finding could suggest that in early adolescence the potential gain associated with low reward gambles is experienced as more rewarding, or that the potential loss associated with the low reward gamble is experienced as less negative. Heart rate changes can help us gain insight into this hypothesis.

Measures of cardiac changes associated with the decision and anticipation of the outcomes of gambles revealed that, consistent with prior studies (Crone, Jennings & Van der Molen, 2004a; Crone & Van der Molen, 2007; Somsen et al., 2000), decisions were associated with anticipatory heart rate slowing, followed by an acceleratory recovery to baseline in all age groups. These cardiac responses have been shown to reflect anticipatory cognitive processes related to a performance monitoring system (Somsen et al., 1985; Van der Molen et al., 1985). When monitoring increases and allocation of attentional resources is required, heart rate typically shows a phasic slowing (Jennings & Van der Molen, 2002). Contrary to our expectations, no difference in the cardiac response to high-risk or low-risk choices was found in any of the age groups.

If it is the case that the youngest participants chose the high-risk gamble for 3 credits more often than the older adolescents because of the way they experience the potential reward, performance monitoring should be increased, since a focus on the potential reward would make the outcome of their decisions more salient. In contrast, when they chose the high-risk gamble associated with low reward more often because of the way they experience the potential loss, performance monitoring should decrease, because the outcome is less salient. Even though high-risk gambles for low reward were not associated with age related differences in cardiac responses, the recovery to baseline was delayed for the 11-12-year-olds for high reward gambles. Heart rate slowed more for these participants, regardless of whether they had chosen a high-risk or low-risk gamble. This finding suggests that, even though participants in all age groups monitor their decisions and anticipate the outcome of their choices, in early adolescence participants are most likely more sensitive to rewards. In addition, this finding supports the hypothesis that younger participants are more willing to gamble because they experience potential rewards differently.

This interpretation is consistent with recent theories on adolescent risk-taking which suggest that early adolescents show more arousal related to potential rewards (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2009; Nelson, Leibenluft, McClure & Pine, 2005). In addition, self-regulatory, or executive skills develop slowly (Huizinga, Dolan & Van der Molen, 2006; Posner & Rothbart, 1998), the larger response to high reward gambles could reflect 11-12-year-olds' immature ability to regulate the arousal they experience in response to the potential reward. An alternative explanation is that because of the slow maturation of executive skills, 11-12-year-olds experience the task differently. They could, for example, find it more difficult to understand that the outcomes of gambles are randomly chosen and that they can not influence the trial sequence. This could result in increased performance monitoring.

Heart rate has also been found to be sensitive to performance feedback, showing more slowing when outcomes are more relevant (Crone et al., 2005a; Crone et al., 2005b). The outcome of gambles were associated with heart rate slowing as well; this slowing was most pronounced for unexpected feedback (losing following a low-risk gamble). Consistent with the findings from our prior studies, heart rate was sensitive to the

informative value of the feedback and not to the valence of the outcome in itself (Crone et al., 2003; Van Leijenhorst et al., 2007). This data pattern again supports our hypothesis that heart rate responses reflect cognitive processes related to an executive control system (Jennings & Van der Molen, 2002; Somsen et al., 2000). No age related differences were observed during the feedback evaluation phase of the task. In this gambling task in which working memory requirements were minimal, and participants did not have to learn from the outcomes of their decisions, heart rate changes showed developmental change until mid adolescence during the anticipation phase of trials, but did not differ between age groups during the outcome processing phase. This finding is consistent with previous studies (Crone & Van der Molen, 2007; Somsen et al., 2000), showing that developmental change in performance monitoring is related to the anticipation of outcomes, not to the processing of outcomes. Moreover, this finding suggests that it is unlikely that adolescents engage in risky behavior because they experience the outcome of their choices differently from adults, but because they weigh the potential reward differently when they make a decision. In early adolescence, participants seem more sensitive to potential rewards. This interpretation fits well with recent theories on adolescent risk-taking based on new insights from studies on functional brain development. These studies show that reward related brain regions (e.g. the ventral striatum) show an enhanced response in adolescence (Ernst et al, 2005; Galvan et al., 2006; Van Leijenhorst et al., 2009), whereas brain regions which are important for cognitive control (e.g. the lateral prefrontal cortices) do not mature until well into young adulthood (Casey, Giedd, & Thomas, 2000; Giedd, 2004; Gogtay et al., 2004). These immature cognitive control abilities paired with the increased sensitivity to reward, are thought to bias adolescents towards risk-taking (Casey, Getz & Galvan, 2008; Ernst, Pine & Hardin, 2006; Steinberg, 2004).

5.4.1 Limitations and future directions

The laboratory context of this study also resulted in several limitations which should be addressed in future studies. First, optimization of the task for autonomic recordings resulted in relatively slow presentation of the stimuli, which made the task less comparable to real-life risk situations. Future studies could further examine the relation between decision-making in a task context and real life risky behavior by looking for correlations with self report measures of risky behavior. In

addition future work could look at the role of performance monitoring as reflected in autonomic nervous system changes by examining the relation between cardiac changes on early trials and decision-making on later trials. Nevertheless, we found a decrease in risk-taking with age, and different reward related anticipatory cardiac responses in the youngest age group. Second, even though participants played for real money, the amount was relatively small (maximum of 4 Euro gain), and gambles were associated with a high or low number of abstract credits. This may have influenced the way in which the different age groups approached the task. While the pattern of heart rate changes suggests that all participants were attentive and were motivated throughout the experiment, 4 Euro could be a more salient reward for participants in the youngest age group. The question how comparable rewards are to participants of different ages cannot be answered with this study, but will have to be addressed in the future. Future studies could explore the subjective emotional reactions of participants to gain insight into their experience of the task. Finally, the brain-based explanations are not based on real brain assessments but are inferred based on the psychophysiological manifestation during separate phases of risk-taking. This approach reveals developmental changes in autonomic nervous system responses to reward in a gambling task, and informs neuroimaging studies on the neural mechanisms of adolescent risk-taking that are currently being conducted in our and other laboratories.

5.4.2 Conclusion

This study contributes to the literature on adolescent decision-making by describing its psychophysiological manifestation in terms of heart rate changes, and providing insight into the temporal resolution of decisions and associated age related differences. The results from this study suggest that developmental differences in reward sensitivity underlie increased risk-taking in adolescence. In particular, the response to rewards during the anticipation of the outcome of risky decisions changes with development, not the response to actual outcomes. These changes could be interpreted as slow maturation of self-regulatory functions which inhibit reward related arousal (Posner & Rothbart, 1998), and are supported by neuroimaging studies which have reported an adolescent specific enlarged response in reward related brain regions in anticipation of outcomes (Ernst et al., 2005; Galvan et al., 2006). Future studies should examine how the development of these systems relates to adolescent risky behavior as it is observed in real-life.

6.

Adolescent risky decision-making: Neurocognitive development of affective and control regions

Recent models hypothesize that adolescents risky behavior is the consequence of increased sensitivity to rewards in the ventral medial (VM) prefrontal cortex (PFC) and the ventral striatum (VS), paired with immature cognitive control abilities due to slow maturation of the dorsal anterior cingulate cortex (ACC) and lateral PFC. We tested this hypothesis with fMRI using a gambling task in which participants chose between Low-Risk gambles with a high probability of obtaining a small reward (1 Euro) and High-Risk gambles with a smaller probability of obtaining a higher reward (2, 4, 6, or 8 Euro). We examined neural responses during choice selection and outcome processing in participants from 4 age groups (pre-pubertal children, early adolescents, older adolescents and young adults). High-Risk choices increased with rewards for all ages, but risk-taking decreased with age for low reward gambles. The fMRI results confirmed that High-Risk choices were associated with activation in VMPFC, whereas Low-Risk choices were associated with activation in lateral PFC. Activation in dorsal ACC showed a linear decrease with age, whereas activation in VMPFC and VS showed an inverted-U shaped developmental pattern, with a peak in adolescence. In addition, behavioral differences in risk-taking propensity modulated brain activation in all age groups. These findings support the hypothesis that risky behavior in adolescence is associated with an imbalance caused by different developmental trajectories of affective and regulatory brain circuitry.

6.1 Introduction

From late childhood until young adulthood, teens increasingly need to rely on their own judgment in potentially risky situations, and they must learn to avoid excessive risks. The ability to make these decisions develops slowly, which can have serious consequences in daily life (Dahl & Gunnar, 2009; Steinberg et al., 2008). For example, self report and observation studies show that the number of traffic accidents peaks in adolescence, and that teens are at risk for getting involved in criminal behavior, experimentation with tobacco and alcohol, and unsafe sexual activity (Furby & Beyth-Marom, 1992; Steinberg, 2004). Even though it is difficult to examine this real-world risk-taking using laboratory tasks, these problems underline the importance of understanding the normal developmental trajectory of decision-making and its contribution to risk-taking behavior.

Tasks measuring decision-making often show a decreases in risk-taking with age (Boyer, 2006), or no age related change in performance after late childhood (Van Leijenhorst, Westenberg & Crone, 2008). However, adolescents show more risky behavior than adults when the experimental task is arousing; for example when peers are present (Gardner & Steinberg, 2005), or when it stresses affective rather than deliberative processing (Figner, Mackinlay, Wilkening, & Weber, 2009). The development of neuroimaging techniques including fMRI has led to neurobiological models that account for these findings by suggesting that risky behavior in adolescence results from the earlier functional maturation of reward-related compared to control-related brain circuitry. Affective and control related circuitry are thought to have separable contributions to decision-making, and the difference in the pattern of their development leads to an imbalance in the adolescent brain (Casey, Getz & Galvan, 2008; Ernst, Pine & Hardin, 2006; Galvan et al., 2006).

In this study, we test this model by examining the development of reward-related and control-related brain regions using fMRI and a gambling task. The developmental neuroimaging studies published to date have revealed that reward processing is associated with activation in similar brain regions in adolescents and adults, including the ventral medial prefrontal cortex (VMPFC) and the ventral striatum (VS) (Bjork et al., 2004; Ernst et al., 2005; Eshel, Nelson, Blair, Pine & Ernst, 2007; Galvan et al., 2006; May et al., 2004). In adults, these regions have been implicated in the processing of primary rewards such as a sweet taste

(McClure, Berns & Montague, 2003; O'Doherty, Deichmann, Critchley & Dolan, 2002), but also in the processing of abstract rewards such as monetary gain (Breiter, Aharon, Kahneman, Dale & Shizgal, 2001; Knutson, Adams, Fong & Hommer, 2001). Developmental studies, have reported stronger activation in the VS in response to rewards in adolescents than in adults (Ernst et al., 2005). Therefore, prior studies have suggested that brain regions associated with reward processing, show a heightened response to rewards in mid-adolescence.

The functional development of cognitive control related brain regions, associated with for example working memory, response inhibition and performance monitoring, typically follows a linear pattern (Casey, Galvan & Hare, 2005; Casey, Giedd & Thomas, 2000). In the context of decision-making tasks, these regions, including the dorsal anterior cingulate cortex (ACC) the dorsal lateral (DL) and ventral lateral (VL) PFC, show developmental changes throughout adolescence (Eshel et al., 2007; Galvan et al., 2006; Van Leijenhorst, Crone & Bunge, 2006). For example, Galvan et al. (2006) found a slow developmental trajectory for the VLPFC/lateral-OFC in a delayed two-choice task in which reward amounts were varied. The extent of activation in this region in response to rewards was larger for 7-11 year olds and 13-17 year olds than for 23-29 year olds. Similarly, Van Leijenhorst et al. (2006) found an age-related decrease in activation in the dorsal ACC associated with an increase in the ability to identify the choice option with the highest probability of resulting in a win between late childhood/ early adolescence (9-12) and young adulthood (18-25). These findings were interpreted as reflecting an immature activation pattern; children and adolescents require more activation in cognitive control related regions than adults when making decisions. In contrast, Eshel et al. (2007) found a decrease in risk-taking together with an increase in activation of the dorsal ACC and VL PFC from adolescence (9-17 years) to adulthood, and interpreted these findings in terms of an increase in the recruitment of cognitive control circuitry with increasing age, resulting in an increase in the ability to regulate impulsive risky behavior. In sum, developmental changes in cognitive control areas during decision-making have been associated with increased as well as decreased neural activation.

To date, the studies on adolescent risk-taking have focused on either the neural correlates of cognitive control (Eshel et al., 2007; Van Leijenhorst et al., 2006), or the neural correlates of reward processing

(Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2009), but have not attempted to directly compare the relative contribution of the brain regions implicated in these processes to adolescent risk-taking behavior. In addition, not all studies have included participants from a wide age range (i.e., children, adolescents and adults), which limits the possibility to test for adolescent-specific patterns of activation and an inverted U-shaped developmental pattern. Therefore, the question whether brain regions associated with reward processing and cognitive control in a risk-taking task follow distinct developmental patterns has not yet been tested explicitly. Also, even though an adolescent specific peak in risky behavior and associated harmful consequences is well documented, not every adolescent engages in real world risky behavior. For example, Galvan, Hare, Voss, Glover & Casey (2007), found a positive relation between self reported risk perception and the response to rewards in the ventral striatum; participants who associated risky behavior with possible negative consequences showed a less pronounced neural response to rewards. Further insight into these individual differences across development is important to identify the adolescents who are at greater risk.

The goal of the present study was twofold: the first goal was to test, using fMRI, whether developmental changes in brain activation related to decision-making under risk can be characterized by a linear development pattern of control related brain regions, including dorsal ACC and lateral PFC, and a peak in adolescence in responsiveness to rewards in reward related regions, including the VMPFC and the VS. The second goal was to test the relation between brain activation and individual differences in risk-taking propensity during development. To test these hypotheses, participants from four age groups (8-10, 12-14, 16-17, 19-22-years old) participated in an fMRI study in which we used a child friendly two-choice decision-making task in which participants repeatedly chose between a low-risk gamble and a high-risk gamble, and in which the amount of reward associated with the high-risk gamble was varied (Van Leijenhorst, Westenberg & Crone, 2008). We tested for different developmental trajectories, by performing high-risk > low-risk gamble comparisons and gain > no-gain outcome comparisons, and by modeling age as a gradually increasing or decreasing predictor or as a non-linear rise-and-fall predictor.

Based on prior empirical studies, and based on the recently postulated models of adolescent risk-taking which suggest an imbalance between

the maturation of control and reward brain circuitry (Casey et al., 2008; Ernst et al., 2006; Steinberg et al., 2008), we predicted that participants would choose the high-risk gamble more often as the reward associated with it increased (Van Leijenhorst et al., 2008). In addition we predicted that rewards would elicit increased activation in VMPFC and the VS, and that activation in these regions would be associated with choices for high-risk gambles (Eshel et al., 2007; Knutson, Wimmer, Kuhnen & Winkielman, 2008). In contrast choices for low-risk gambles were expected to be associated with increased activation in lateral PFC regions (Eshel et al., 2007). We further predicted that the neural response in reward related regions and control related regions would co-vary with individual differences in risk-taking propensity. With regard to development, we expected that 1) when both choice options are similar, decision-making in younger participants would be associated with increased activation in dorsal ACC (Van Leijenhorst et al., 2006), 2) that high potential reward would be associated with a peak in activation of reward related regions in the VS and VMPFC in mid-adolescence, during both the decision and outcome phase (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2009), and 3) that activation in control related regions in lateral PFC would show a linear change in activation with age (Eshel et al., 2007; Galvan et al., 2006).

6.2 Method

6.2.1 Participants

Fifty-eight healthy, right-handed volunteers were included in the study. To dissociate developmental changes related to puberty and adolescence, we recruited participants from four age groups; thirteen pre-pubertal children (aged 8-10 years; 8 female; mean age 9.7, SD = 0.9), fifteen pubertal adolescents (aged 12-14 years; 8 female; mean age 13.4, SD = 0.8), fifteen post-pubertal adolescents (aged 16-17 years; 7 female; mean age = 17.1, SD = 0.7), and fifteen young adults (aged 19-26 years; 7 female; mean age = 21.6, SD = 2.08). All procedures were approved by the Leiden University Department of Psychology and the Medical Ethical Committee at the Leiden University Medical Center. All participants, or a primary caregiver in the case of minors, gave informed consent. Data for two additional participants (an 8-year-old and a 21-year-old) was excluded from the analyses because of excessive head movement. Mean head movement was .14 mm for the 8-10 year olds, .08 mm for the 12-14 year olds, .07 mm for the 16-17

year olds, and .06 mm for the 19-26 year olds. Even though mean head movement during scanning was slightly higher in the youngest age group than in the older the age groups (F (3, 57) = 12.10, $p < .001$), for none of the participants head movement during scanning exceeded 1 voxel in any direction. Participants in the three youngest age groups were screened for behavioral problems using parent-ratings on the Child Behavior Checklist (Achenbach, 1991). Scores for all participants fell within the non-clinical range.

6.2.2 The Cake Gambling Task

The present study used an adapted version of a child friendly gambling task (Van Leijenhorst et al., 2008) in which participants were asked to choose between a low-risk gamble and a high-risk gamble associated with a probabilistic monetary reward. In this gambling task, all information that was relevant for making a decision was presented to participants on every trial and no information had to be learned or retrieved over consecutive trials. The probability associated with both gambles and the associated potential rewards were presented visually. Participants saw a cake composed of six brown and pink wedges in a 4:2 ratio (see Figure 6.1A) and a pink and brown square presented at the bottom of the screen in which the reward associated with that color was presented as stacks of 50 cent coins. On each trial, one of the wedges was randomly selected by the computer. If the color of this wedge matched the color that the participant chose, the reward associated with that gamble was won; if they did not match, the gamble did not result in a reward. Participants chose between a low-risk gamble (betting on the majority color with a 66 % chance of winning) and a high-risk gamble (betting on the minority color with a 33 % chance of winning). The probabilities associated with the two choice options were kept constant but the amount of reward associated with the high-risk gamble was varied. The potential reward associated with the low-risk gamble was always 1 Euro, whereas the potential reward associated with the high-risk gamble was 2, 4, 6, or 8 Euro. The condition in which a choice had to be made between a 1 Euro low-risk gamble and a 2 Euro high-risk gamble was ambiguous, since the expected value (the probability x reward magnitude) of both choice options was equal. In the conditions in which the high-risk gamble was associated with 4 to 8 Euro, the expected value of the high-risk gamble was always higher than that of the low-risk gamble. Trials had the following structure: a fixation cross was presented for 500 ms, followed by the presentation of the cake

stimulus which remained visible for 2000 ms. During this time, participants had to make their choice via a button press with the index or middle finger of their right hand. Following the cake stimulus, a fixation cross was presented for 4000 ms after which participants were shown the outcome of the gamble for 2000 ms.

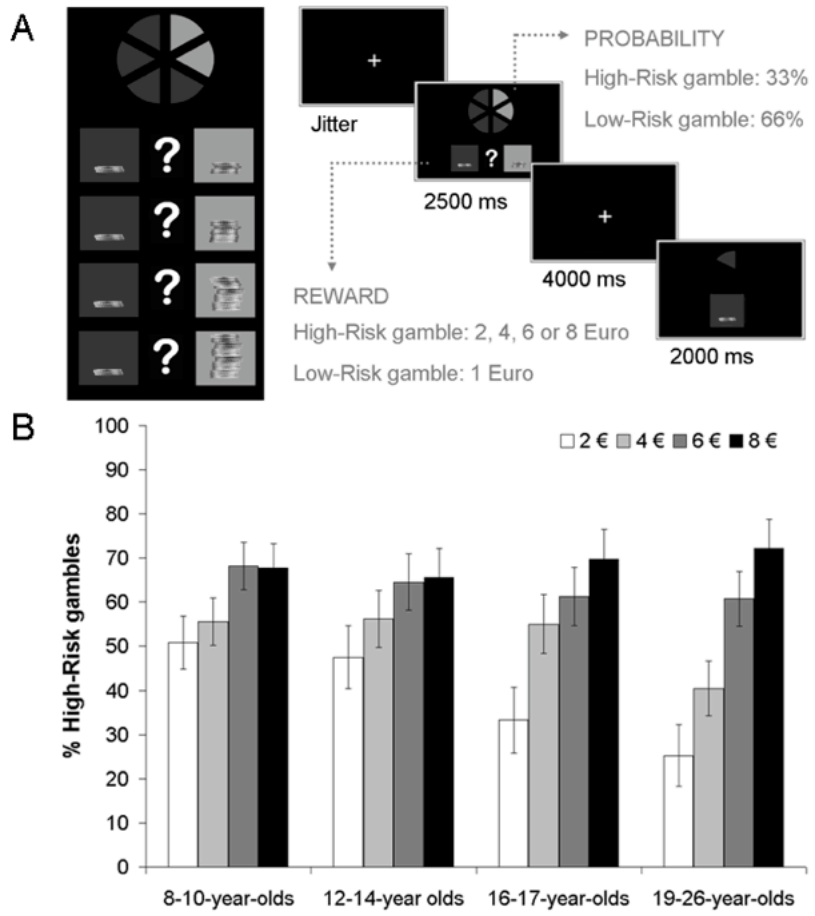

Figure 6.1 *A) The Cake Gambling Task. The left panel shows the different trial types as a function of the amount of reward associated with the High-Risk gamble. The right panel depicts trial timing for an example of a low-risk choice followed by a gain outcome. B) Behavioral Results, the percentage of choices for the High-Risk gamble shown for each Reward condition (2, 4, 6 and 8 Euro), and Age group (8-10-year-olds, 12-14-year-olds, 16-17-year-olds, and 19-26-year-olds). Error bars depict standard error. Age differences were only present for the 2-Euro condition.*

The outcome screen indicated the result of the gamble (gain or no-gain) as well as the size of the associated reward. For gain outcomes, participants saw the stack of coins they had gambled with. For no-gain outcomes, participants saw this stack of coins with a cross through it. Jittered fixation varying between 300 ms and 5250 ms in increments of 550 ms was added to the inter trial intervals using an optimization program (optseq2; see http://surfer.nmr.mgh.harvard.edu/optseq/, developed by Dale, (1999)).

6.2.3 Raven Standard Progressive Matrices

All participants completed Raven's Standard Progressive Matrices (Raven, Raven & Court, 1998) outside of the scanner in order to obtain an estimate of their ability to form perceptual relations and reason by analogy. The Raven Standard Progressive Matrices (RSPM) is a non-verbal test designed to measure general intellectual ability (Raven et al., 1998). Based on the final scores on this test, we obtained estimated IQ scores using Dutch norms. Estimated mean IQ scores all fell within the average to high-average range; 123.31 (SD = 7.86) for the 8-10 year olds, 120.60 (SD = 10.87) for 12-14 year olds, 115.20 (SD = 10.36) for 16-17 year olds, and 125.33 (SD = 7.28) for 19-26 year olds. Estimated IQ scores for 16-17 year olds were the lowest. However, only the difference between 16-17 year olds' estimated IQ scores and 19-26 year olds' estimated IQ scores reached significance ($F(1, 28) = 9.61$, $p < .01$). Because all participants' scores fell within the average to high-average range, IQ differences are not described further.

6.2.4 Procedure

Participants were prepared for the scan in a quiet laboratory. A mock scanner was used to simulate the environment and sounds of an actual MRI scanner. All participants received extensive instructions and performed 11 practice trials immediately before the scan. They were told that their goal was to win as often as possible and that at the end of the experiment they would get to keep the sum of two randomly selected outcomes (one trial per task block). We explained that there was no need to remember performance on previous trials because trials were not related, and that each trial could be chosen in the end. Therefore, all trials were equally important. We explained that gambling requires some luck, and that their winnings could be anywhere between 0 and 16 Euro. In reality, all participants were paid 5 Euro. Following

the scan, participants filled out the RSPM, and additional questionnaires which are not reported here.

6.2.5 MRI Data Acquisition

In total, 84 trials, with 21 trials per condition, were presented over the course of two event-related scans that lasted approximately 7 minutes each. Scanning was performed using a standard whole-head coil on a 3 Tesla Philips scanner at the Leiden University Medical Center (LUMC). Stimuli were projected onto a screen that participants could see via a mirror attached to the head coil. Functional data were acquired using a T2*-weighted gradient-echo echo-planar pulse sequence (38 contiguous 2.75 mm oblique axial slices, using sequential acquisition, TR = 2.2 s, TE = 30 ms, 2.75 x 2.75 mm inplane resolution, 200 volumes per run). High-resolution T2* weighed images and high resolution T1 anatomical images were collected at the end of the scan session. Head motion was restricted using a pillow and foam inserts that surrounded the head. Participants watched cartoons while structural scans were collected.

6.2.6 fMRI preprocessing and Statistical analysis

Data pre-processing and analysis was conducted using SPM5 (Wellcome Department of Cognitive Neurology). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Functional volumes were spatially normalized to echo planar imaging templates. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan & Evans, 1997). The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization the data was resampled to 3 mm cubic voxels. Functional volumes were smoothed with a 6 mm full-width at half maximum isotropic Gaussian kernel.

Statistical analyses were performed on individual subjects' data using the general linear model implemented in SPM5. For each participant, the fMRI time series were modeled as a series of zero duration events convolved with a canonical hemodynamic response function (HRF). We modeled the onset of the stimulus and the onset of the outcome of each trial as zero duration events. Trials for which no response was given within the 2000 ms cue window were modeled separately and were excluded from subsequent analyses. Decision-analyses related to the

stimulus distinguished high-risk and low-risk gambles for the four different reward conditions (2, 4, 6, and 8 Euro gambles). Outcome-analyses distinguished gain and no-gain outcomes for the four reward conditions (2, 4, 6, and 8 Euro) following high-risk gambles; gain and no-gain outcomes following a low-risk gamble were modeled separately. The modeled events were used as covariates in a general linear model, along with a basic set of cosine functions that high-pass filtered the data. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. The resulting contrast images, computed on a subject-by-subject basis, were submitted to group analyses. At the group level, whole-brain contrasts between conditions were computed by performing one-tailed t-tests, treating participants as a random effect. Task-related responses were considered significant if they exceeded an uncorrected threshold of $p < .001$, with an extent threshold of 10 voxels.

To test the hypothesis that control related regions followed a linear increase or decrease with development, whereas reward related regions followed a nonlinear trend and showed a peak in adolescence, we performed separate voxelwise ANOVAs. These analyses aimed at identifying regions that showed age-related change in activation related to decision-making and during outcome processing. We tested for both linear (-3 -1 1 3 / 3 1 -1 -3 contrast) and quadratic (-1 1 1 -1 contrast) age-related patterns of change. ANOVAs were also considered significant if they exceeded an uncorrected threshold of $p < .001$, and an extent threshold of 10 contiguous voxels.

6.2.7 fMRI Results: Region of Interest Analysis

We used the MarsBaR toolbox for use with SPM5 (MarsBaR; see http://marsbar.sourceforge.net/ developed by: Brett, Anton, Valabregue & Poline (2002)) to perform region of interest (ROI) analyses to further illustrate patterns of activation in the clusters that we identified in the voxelwise analyses. We created 6 mm spherical ROIs centered at the peak active voxel for these clusters.

6.3 Results

6.3.1 Risk-taking behavior and Reaction Times (RTs)

We submitted the percentage of High-Risk gambles to a repeated

measures ANOVA with Age group as between subjects factor and Reward (2, 4, 6, 8 Euro) as within subjects factor. Risk-taking increased when the reward at stake was higher (main effect Reward, F (3, 162) = 39.13, $p < .001$). On average, risk-taking did not differ between age groups ($p = .51$), but there was a significant Age group x Reward interaction (F (9, 162) = 2.57, $p < .005$) (see Figure 6.1B.). Follow-up ANOVAs for the age groups separately showed that participants in all age groups made more High-risk decisions as rewards increased (all p's $< .005$). However, comparing the age groups in each reward condition separately showed no age-related differences in the percentage of High-Risk decisions for the 4, 6, and 8 Euro gambles (p's $> .1$). In contrast, for 2 Euro gambles this analysis revealed a decrease in risk-taking with age ($p < .05$), suggesting that in the most ambiguous condition older participants were more risk averse. Post hoc ANOVAs confirmed that the percentage of risk-taking in the 2-Euro condition was higher for 8-10-year-olds and 12-14-year-olds relative to 19-26-year-olds, whereas the 16-17-year-olds did not differ from the younger and older age groups.

To test for age-related differences in response times, we submitted participants' average RTs to a repeated measures ANOVA with Reward (2, 4, 6, or 8) and Choice (High-Risk, Low-Risk) as within subjects factors and Age group as between subjects factor. Ten participants were excluded from this analysis due to missing observations in one or more of the conditions (2 pre-pubertal children, 1 pubertal adolescent, 4 post-pubertal adolescents, and 3 young adults). The analysis showed that average RTs did not differ between Age groups ($p = .21$), or between High-Risk and Low-Risk decisions ($p = .33$). RTs varied as a function of the amount of reward at stake as revealed by a main effect of Reward (F (3, 132) = 4.68, $p = .004$). RTs for 2 Euro gambles were slower compared to 6 Euro ($p < .05$) or 8 Euro ($p < .001$) gambles. This pattern of results did not differ as a function of Age (Reward x Age Group, $p = .36$) (see Supplemental Figure 6.1).

Taken together, there were no age differences in risk-taking when the reward at stake was high, however, for the more ambiguous 2 Euro gambles participants were more risk averse as they were older. There were no age differences in response times, suggesting that age differences in neural responses cannot be explained by differences in reaction times or impulsive responding.

6.3.2 fMRI results

The fMRI results are described in two sections; first we describe the results of the analyses during the decision phase, then we describe the analyses related to the outcome processing.

6.3.3 Brain regions involved in High-Risk versus Low-Risk decisions

We first identified brain regions underlying risk-taking behavior across age groups. We performed a general linear model analysis on the functional data modeled at the onset of the stimulus, and computed a voxelwise contrast of High-Risk > Low-Risk decisions across reward conditions. This analysis revealed three significant clusters in the medial PFC; one cluster in the dorsal medial PFC (peak at -12, 51, 18, z = 3.62) , $t(1, 57) = 3.85$, $p < .001$, one in the ventral medial PFC (peak at -6, 60, -6, z = 3.96) , $t(1, 57) = 4.26$, $p < .001$, and one cluster in the subgenual ACC (peak at -3, 21, -6, z = 4.34) , $t(1, 57) = 4.75$, $p < .001$. The reverse contrast of Low-Risk > High-Risk decisions resulted in a cluster of activation in right DLPFC (peak at 39, 24, 36, z = 4.49), $t (1, 57) = 4.94$, $p < .001$ (see Figure 6.2A). These results are consistent with the dual process hypothesis which suggests that activation in reward related areas in the medial PFC is associated with risky decisions, whereas activation in control areas in the lateral PFC is associated with cautious decisions. All significant clusters and corresponding MNI coordinates are reported in Supplemental Table 6.1.

6.3.4 Effects of reward magnitude on risk-taking

Second, we tested which brain regions involved in risk-taking were modulated by the amount of reward at stake. We performed voxelwise ANOVAs testing for linear changes in activation as a function of reward size on the High-Risk > Low-Risk contrast across participants. The ANOVA testing for a linear increase in activation as a function of increasing reward (-3 -1 1 3 contrast) revealed significant clusters of activation in the right putamen (peak at 24, 15, 3, z = 4.40), $t(1, 212) = 4.51$, $p < .001$, and bilateral amygdala (peaks at -24, 0, -18, z = 3.88 and 15, -6, 18, z = 3.59), $t(1, 212) = 3.95$, $p < .001$ and $t(1, 212) = 3.65$, $p < .001$, respectively (see Figure 6.2B). The ANOVA testing for a linear decrease in activation as a function of the amount of reward (3 1 -1 -3 contrast) did not result in any significant clusters. These analyses are consistent with the hypothesis that subcortical affective areas are

sensitive to the reward that is associated with a risk. All significant clusters and corresponding MNI coordinates are reported in Supplemental Table 6.2.

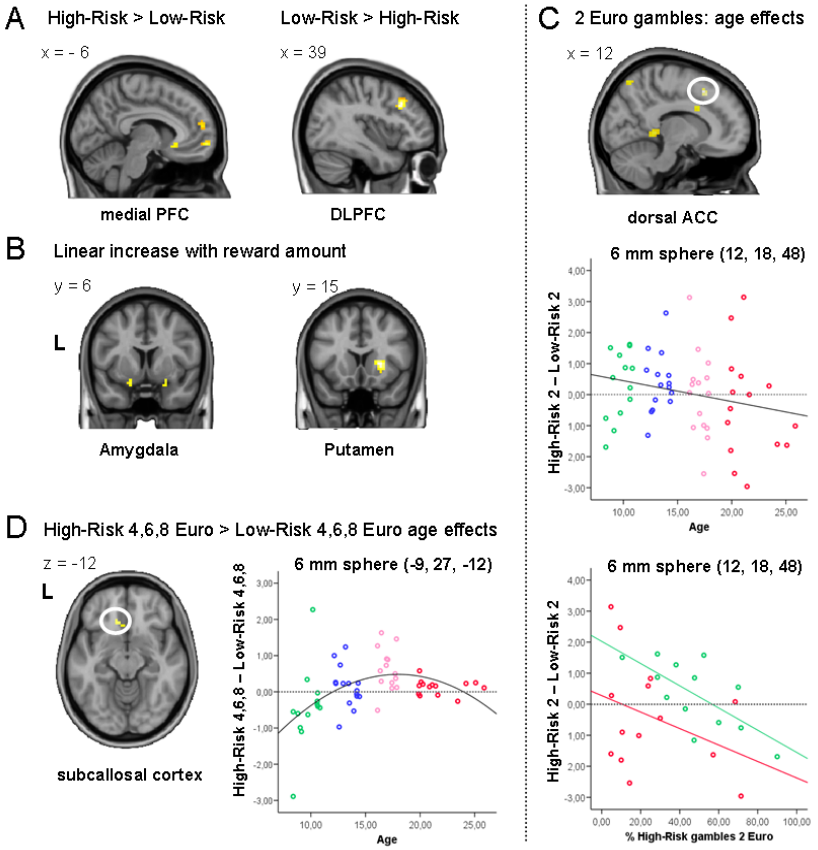

Figure 6.2 *A) Whole-brain results for the contrast of High-Risk and Low-Risk gambles for all participants combined modeled at the time the gamble options were presented. B) Regions for which the contrast of High-Risk > Low-Risk gambles showed a parametric increase with the amount of reward. C) Dorsal ACC region which showed a linear decrease with age in the 2 Euro condition, when corrected for individual differences in risk-taking (top scatter plot), and plotted for the children (green) and adults (red) as a function of risk-taking in the 2 Euro condition (bottom scatter plot). D) Region which shows an adolescent specific peak in activation for the High-Risk > Low-Risk contrast for high reward (4, 6, and 8 Euro) gambles combined. All images are thresholded at p < .001 uncorrected, 10 contiguous voxels. In scatter plots, data for 8-10-year-olds is presented in green, for 12-14-year-olds in blue, for 16-17-year-olds in pink, and for 19-26-year-olds in red.*

6.3.5 Neural correlates of age-related differences in risk-taking

To identify age-related differences in brain regions associated with risk-taking, we modeled a linear increase (-3, -1, 1, 3), linear decrease (3, 1, -1, -3) and adolescent specific peak (-1 1 1 -1) as a function of Age group. We first tested these patterns in an ANOVA for High-Risk > Low-Risk decisions across all reward conditions. The linear decrease ANOVA resulted in a small cluster of activation in the dorsal ACC (peak at 12, 9, 27, z = 3.90), $t(1, 54) = 4.22$, $p < .001$, and a larger cluster in the central opercular cortex/postcentral gyrus (peak at 51, -6, 21, z = 4.44), $t(1, 54) = 4.90$, $p < .001$. No regions showed a linear increase with age or a peak in adolescence. Second, because we only found age-related differences in performance in the 2 Euro condition, but not in the higher reward conditions, we repeated these ANOVAs for the 2 Euro condition separately and for the higher reward conditions (4, 6, 8 Euro) combined.

Contrary to our expectations, the analysis for the 2 Euro condition did not result in any significant clusters when testing for age differences. However, the significant differences in performance between the age groups in the 2 Euro condition could be a confounding factor. When we added the percentage of High-Risk gambles in the 2 Euro condition as a covariate factor to the ANOVA, we found a significant cluster in the dorsal ACC (peak at 12, 18, 48, z = 3.83), $t(1, 54) = 4.14$, $p < .001$ (see below for performance regressions, and Figure 6.2C), but only at a lower threshold ($p < .005$). The relation between age versus performance is described in more detail below.

The same analysis for the higher reward conditions mirrored the results found for all reward amounts combined, showing a linear decrease with age in the same regions in the dorsal ACC (peak at 12, 9, 27, z = 4.46), $t(1, 52) = 4.95$, $p < .001$, and central opercular cortex (peak at 54, -3, 12, z = 4.41), $t(1, 52) = 4.88$, $p < .001$. Again no regions showed a linear increase with age, but for these high reward conditions (4, 6 and 8 Euros combined) we found a small cluster in the medial OFC/ subcallosal cortex which showed a peak in activation for adolescents compared to children and adults (peak at -9, 27, -12, z = 3.55), $t(1, 52) = 3.80$, $p < .001$ (see Figure 6.2D). All significant clusters and corresponding MNI coordinates are reported in Supplemental Table 6.3. The results of the analyses comparing the different age groups from late childhood through early adulthood are consistent with the hypothesis

that risky decisions are associated with more ACC activation in children, and with the hypothesis that risk-taking is associated with more activation in affective areas within the VMPFC in adolescents compared to children and young adults, but only when gambles are associated with a high potential reward.

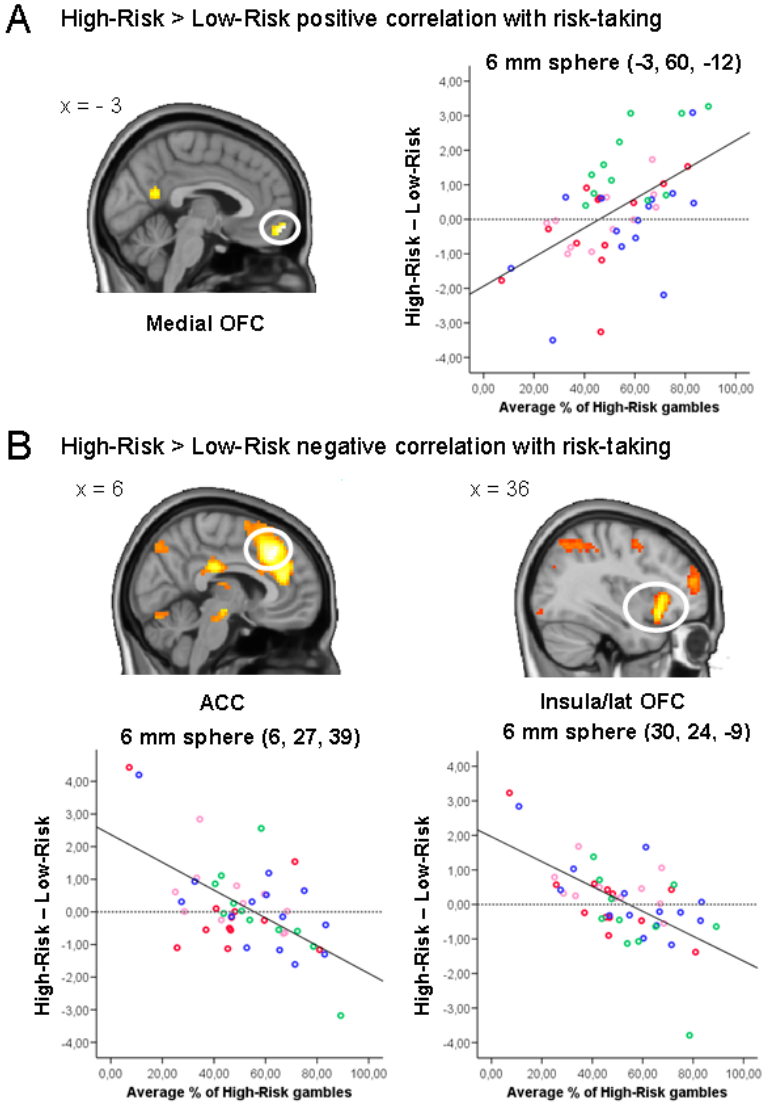

Figure 6.3 *A) Clusters of activation in the ventral medial PFC/medial OFC that show a positive correlation with risk-taking. B) Clusters of activation in dorsal ACC and Insula that show a negative correlation with risk-taking. All images are thresholded at p < .001 uncorrected, 10 contiguous voxels. In scatter plots, data for 8-10-year-olds is presented in green, for 12-14-year-olds in blue, for 16-17-year-olds in pink, and for 19-26-year-olds in red.*

6.3.6 Individual differences in Risk-taking

More detailed analyses on individual participants' behavioral data revealed that there were large individual differences in risk-taking within all age groups (see Supplemental Figure 6.2 for scatter plots). The second goal of this study was therefore to identify brain regions that contribute to these individual differences in the tendency to gamble. To this end, we added the average percentage of High-Risk choices as a regressor to the analysis on the contrast of High-Risk > Low-Risk decisions.

As can be seen in Figure 6.3A, one region in the ventral medial PFC (peak at -3, 60, -12, z = 5.07), $t(1, 56) = 5.74$, $p < .001$, was more active in the High-Risk > Low-Risk contrast for those participants who chose the High-Risk gambles more often. In contrast, a large region in the dorsal medial PFC (with sub-clusters in the paracingulate gyrus; peak at 6, 27, 39, z = 6.13, $t(1, 56) = 7.36$, $p < .001$; and ACC; peak at 9, 36, 18, z = 5.49, $t(1,56) = 6.35$, $p < .001$), showed the opposite pattern; this region was more active in the High-Risk > Low-Risk contrast for individuals who chose the Low-Risk gambles more often (see Figure 6.3B). The latter contrast also showed increased activation in bilateral DLPFC, lat-OFC/Insula, and parietal cortex[1] (see Supplemental Table 6.4 for coordinates).

Together, the results are consistent with the hypothesis that activation in reward related areas within the medial PFC co-varies with risk-taking behavior, whereas activation in control areas in dorsal medial PFC and lateral PFC co-varies with risk-averse behavior[2].

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[1] Additional analyses for the regions that were found in the general High-Risk vs. Low-Risk contrast (dorsal medial PFC, ventral medial PFC and subgenual ACC for High-Risk > Low-Risk and DLPFC for Low-Risk > High-Risk) showed that the ventral medial PFC cluster (peak at -6, 60, -6), which partly overlaps with the ventral medial PFC area identified in this regression analysis, showed a positive correlation with risk-taking as well.

[2] The pronounced brain-behavior relations may explain why the developmental differences in the 2 Euro condition above could not be revealed; possibly, in this condition individual difference in performance are a stronger predictor of brain activity than differences in age. It should be noted that the correlation of risk-taking in the 2 Euro condition and average risk-taking across all reward conditions was high ($r = .56$, $p < .001$), therefore, the same analyses for the 2 Euro condition mirror the effects across reward conditions.

6.3.7 Brain regions related to the processing of outcomes of High-Risk gambles

To identify regions which respond to the receipt of a reward following High-Risk gambles, we performed a GLM analysis on the functional data modeled at the onset of the outcome, and computed the voxelwise contrast of Gain > No-Gain outcomes following High-Risk decisions across age groups. This analysis revealed large clusters of activation in the medial PFC and ventral striatum (see Figure 6.4A). The peak active voxel for the medial PFC cluster was located more ventral (peak at -3, 45, -6, z = 6.27), $t(1, 43) = 8.08$, $p < .001$, and in addition we located a more dorsal sub-cluster (peak at 6, 51, 3, z = 6.37) , $t(1, 43) = 8.29$, $p < .001$. Activation in the ventral striatum peaked in the left NAcc (peak at -9, 9, -9, z = 5.73), $t(1, 43) = 7.08$, $p < .001$, and right NAcc (peak at 9, 15, -6, z = 6.30, $t(1, 43) = 8.14$, $p < .001$. No significant clusters were found for the reverse No-Gain > Gain contrast. All clusters and corresponding MNI coordinates are reported in Supplemental Table 6.5.

6.3.8 Effects of reward magnitude on outcome processing

To identify brain regions which respond to parametric changes in the amount of reward, we tested for a linear change in activation as a function of increasing reward (-3 -1 1 3 contrast) in voxelwise ANOVAs on the Gain > No-Gain outcome contrast. The ANOVA testing for a linear increase in activation revealed significant clusters in the right putamen (peak at 24, 9, 0, z = 3.01 t (1, 209) = 3.05, $p = .001$ and right VS/NAcc (peak at 9, 6, -12, z = 3.51 t (1, 209) = 3.57, $p < .001$ (see Figure 6.4B). The ANOVA testing for a linear decrease in activation as a function of the amount of reward associated with the decision (3 1 -1 -3 contrast) did not result in any significant clusters.

6.3.9 Neural correlates of age-related differences in outcome processing

Our final analyses tested for age-related differences in neural responses to the outcome of High-Risk gambles (see Supplemental Figure 6.3 for Gain > No-gain contrast plotted for the age groups separately). We tested for three patterns of age-related change: linear increase (-3, -1, 1, 3), linear decrease (3, 1, -1, -3) and a peak in adolescence (-1 1 1 -1) on the Gain > No-Gain outcomes across reward amounts. No regions were found that showed a linear change with development. In contrast, the peak model revealed activation in the caudate (peak at 21, 18, 9, z =

3.26 $t(1, 40) = 3.52$, $p = .001$) (see Figure 6.4C.), suggesting a peak in the responsiveness of this region to gains in adolescence.

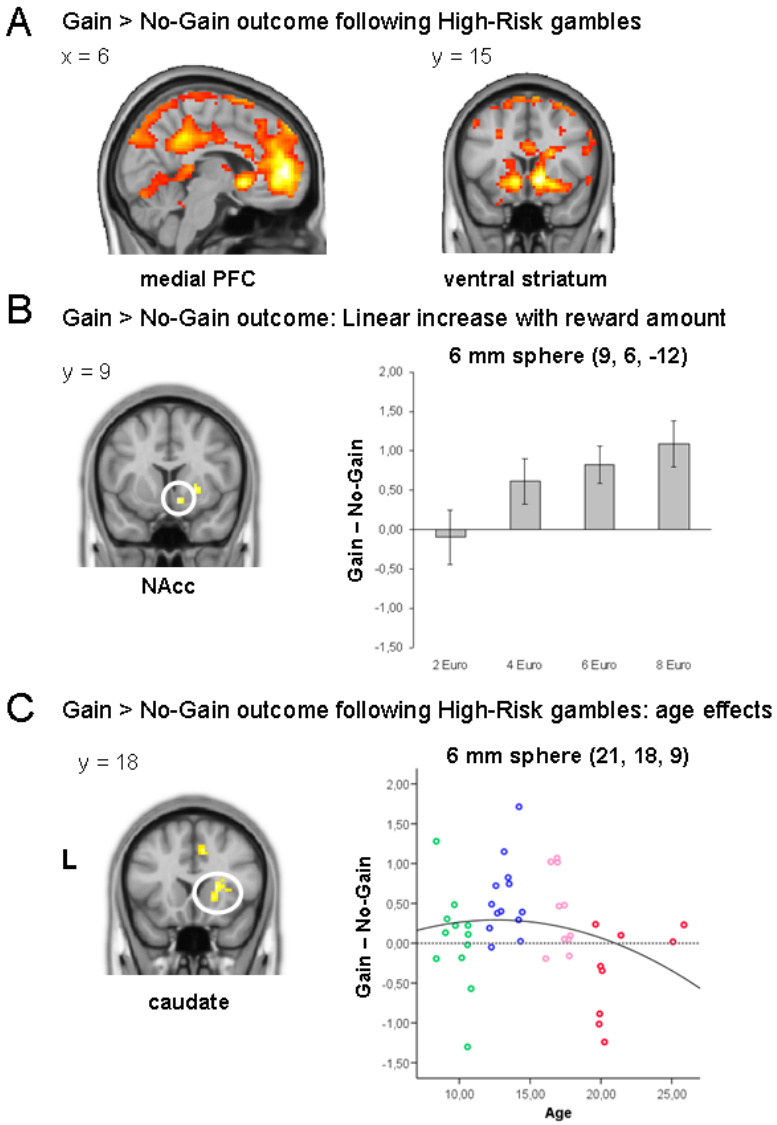


Figure 6.4 *A) Whole-brain results for the contrast of Gain > No-Gain outcomes following High-Risk decisions for all participants combined modeled at the time the outcome was presented. B) Regions for which the contrast of Gain > No-Gain outcomes showed a parametric increase with the amount of reward. C) A region in the ventral striatum showed an adolescent specific peak in activation for the Gain > No-Gain contrast. All images are thresholded at p < .001 uncorrected, 10 contiguous voxels. In scatter plots, data for 8-10-year-olds is presented in green, for 12-14-year-olds in blue, for 16-17-year-olds in pink, and for 19-26-year-olds in red.*

Together, the results from the outcome analyses are consistent with the hypothesis of increased activation in the striatum for gain outcomes, and with the hypothesis that this region is more responsive in mid-adolescence.

6.4 Discussion

The main goal of this study was to test for two different patterns of functional brain development that have been proposed to account for adolescent risk-taking: an inverted U-shaped pattern for reward related regions with a peak in adolescence, and a linear pattern for regions associated with cognitive control. Recent models of adolescent risk-taking have described risk-taking in adolescence as a consequence of these different developmental trajectories (Casey et al., 2008; Ernst et al., 2006; Steinberg et al., 2008). Behaviorally, we found no age-related differences in risk-taking behavior for gambles associated with high rewards; all participants were more likely to take risks as the potential reward increased. These results are consistent with prior studies which showed that the ability to incorporate reward and probability information in decisions under risk is already mature by late childhood (Van Leijenhorst et al., 2008). Interestingly we found a linear decrease in risk-taking for ambiguous gambles; when the expected values of two choices were equal, and both options were associated with low reward, adults preferred to choose the low-risk gamble, whereas younger participants were more likely to choose the high-risk gamble. The finding that adults are risk averse in ambiguous risky situations is consistent with studies that have shown that adults often make risk-averse decisions in the context of potential gains (Tversky & Kahneman, 1981), and with dual process models such as "Fuzzy-trace theory" (Reyna & Rivers, 2008). The latter theory offers an explanation for this finding by proposing that adult decision making in ambiguous situations is dependent on intuitive, rather than computational processes. This intuitive decision-making is thought to develop slowly, and because of this slow development, children rely more on computational strategies when making decisions, and their choices can therefore appear more rational (Reyna & Ellis, 1994; Rivers, Reyna & Mills, 2008).

The fMRI data associated with the decision and outcome phase of gambles resulted in two main findings: First, across ages, risky choices were associated with activation in the medial PFC and the ventral

striatum, whereas cautious choices were associated with activation in the lateral PFC. These results support the hypothesis that the relative weight of reward related regions (medial PFC and ventral striatum) and cognitive control related regions (lateral PFC) contributes to decision-making under risk, in such a way that more activation in reward related regions is associated with risk-taking, whereas more activation in control related regions is associated with cautious behavior. Second, the results of our tests for linear and non-linear age-related changes are consistent with the hypothesis that the relative weight of control related regions and reward related regions changes across development (Casey et al., 2008; Ernst et al., 2006; Galvan et al., 2006; Steinberg et al., 2008), and are in favor of models that hypothesize that risky behavior in adolescence is a consequence of the different developmental trajectories for reward related and control related brain regions (Casey et al., 2008; Galvan et al., 2006; Steinberg et al., 2008).

6.4.1 Control related changes

Consistent with the prediction that cognitive control regions follow a linear change with development, we found a linear decrease in activation with age associated with risky choices in the dorsal ACC. This is consistent with our earlier finding that this region was more active in 9-12 year old participants compared to adults when participants had to identify the most likely outcome in a two-choice task which measured the ability to judge probability (Van Leijenhorst et al., 2006). The finding that there is more activation in control related regions in children and adolescents compared to adults is also consistent with the results reported by Galvan et al. (Galvan et al., 2006) who found a linear decrease in activation in the VLPFC with age in a delayed two-choice task in which reward amounts were varied, and with the finding that activation in regions related to cognitive control often shows a shift from diffuse to focal activation (Durston et al., 2006).

A different pattern, however, was reported by Eshel and colleagues (2007), who used a similar paradigm to the one used in the present study. Eshel et al found more activation in the dorsal ACC and VLPFC for risky choices together with less risky behavior in adults compared to adolescents. These authors interpreted this increase in activation in these regions as reflecting an increased recruitment of cognitive control related regions associated with the regulation of risky decisions. One explanation for these contrasting findings could be found by examining

differences in the tasks that have been used. First, we aimed to control for differences in working memory ability between children, adolescents and adults by instructing participants that trials were not related and that therefore participants would not have to remember their choices and the outcomes of previous trials. In addition, participants were told that only two gambles would be randomly chosen by the computer at the end of the experiment that would determine their prize money. In contrast, in the Eshel et al study participants were paid based on their cumulative earnings; increased recruitment of ventral PFC regions and ACC could reflect differences in the strategies used by adolescents and adults in the context of these different task demands. Second, we only varied the amount of reward associated with the high-risk gamble but not the probabilities associated with both choice options; in all high-reward conditions the high-risk gamble was also associated with the highest expected value. In the Eshel et al. study, both the probability and the magnitude of reward was varied, and importantly, the expected value of the low-risk choice option was higher than that of the high-risk choice option. It is possible that in the Eshel et al. study adults had a more accurate representation of the expected value associated with the two choice options (Levin, Weller, Pederson & Harshman, 2007), and consequently chose the options with the highest expected value more often (which were the low-risk choices). Possibly, activation in ACC and VLPFC could reflect processes important for forming this reward representation. For example, Smith et al. (2009) adapted the task used by Eshel et al (2007), and demonstrated that different PFC regions specifically respond to reward, risk and probability. That is, regions in the VMPFC responded to reward, and activation in dorsal ACC was interpreted in terms of response conflict.

The decrease in ACC activation with age observed in the present study could reflect a decreased need for cognitive control with increasing age. No regions showed a linear increase in activation with age, this finding could be interpreted as a reflection of the relatively low task demands in the current study. In all age groups, DLPFC activation was associated with low-risk choices. Even though DLPFC is one of the last regions to mature both structurally (Gogtay et al., 2004) and functionally (Bunge & Wright, 2007), the finding that the different age groups do not differ in recruitment of this region is consistent with previous studies. These have shown that children recruit lateral PFC regions and perform similar to adults when task demands are low, but differ from adults when the task is more difficult (Crone, Wendelken, Donohue, Van

Leijenhorst & Bunge, 2006). In future studies it would be interesting to examine developmental changes in the effects of task difficulty and working memory demands on the recruitment of control related circuitry in a decision-making context (Geier & Luna, 2009).

6.4.2 Reward related changes

Consistent with the prediction that reward related regions follow a non-linear change with development, a region in VMPFC and in the VS showed a peak in activation in adolescence, both during the decision phase of trials and during the outcome phase. This is the first study to report this peak in relation to risky choices in a decision-making paradigm. The Galvan et al. (2006) study compared children (7-11 years), adolescents (13-17 years) and adults (23-29 years), but used a delayed response two-choice task in which participants did not have to weigh probabilities and rewards. The Eshel et al. (2007) study did use an active gambling task, but these researchers only compared adolescents to adults, which did not enable them to test for a peak in brain responsiveness to risk and reward in adolescence. The comparison of adolescents and adults did not result in differences between these age groups in activation in the VS during the decision phase (Eshel et al., 2007). However, the processing of reward outcomes in these participants was associated with more activation in the VS in adolescents compared to adults (Ernst et al., 2005). These finding are consistent with prior results, showing that the neural response to rewards is larger during the outcome phase of trials than during the decision phase (Van Leijenhorst et al., 2009). Finally, the brain region that showed a peak in activation in adolescence during the decision phase was more anterior (VMPFC/subcallosal cortex) compared to the region that showed this peak during the outcome phase (VS/caudate).

6.4.3 Individual differences

One interesting finding in the current experiment is that the behavioral data do not reveal a peak in risk-taking in adolescence. This finding is not uncommon, other studies have also failed to report this peak behaviorally (Van Leijenhorst et al., 2008), and more often linear changes in risk-taking behavior (Crone, Bullens, Van der Plas, Kijkuit & Zelazo, 2008) are reported (see also Boyer (2006) for a review). These findings reflect the difficulty of showing deviant adolescent behavior in a controlled experimental setting. Importantly, when

differences in behavior are small, or even absent, fMRI can reveal a difference in the neural correlates of this behavior across development and can help build hypotheses. To better understand the relation between risk-taking behavior as it is observed in everyday life and the developmental changes in brain circuitry important for decision-making observed in the laboratory, future studies could benefit from examining how individual differences in behavior relate to changes in brain function across development.

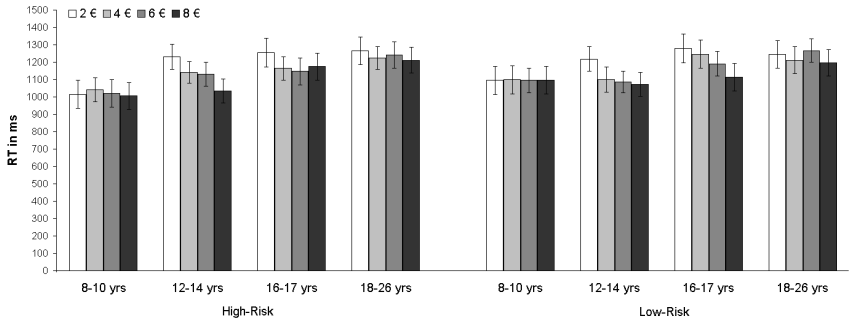
In the present study individual differences in risk-taking behavior in the task were associated with activation in regions in medial PFC, and not with activation in the VS. Interestingly, activation in control related regions in dorsal medial PFC showed a negative correlation with risk-taking behavior, whereas activation in reward related regions in VMPFC showed a positive correlation with risk-taking. These findings suggest the possibility that the function of these regions is associated with participants' behavioral preferences. A similar dissociation between dorsal and ventral MPFC regions activation in relation to risk preference in adults has been reported recently by Xue et al. (2009). These authors suggest that a strong reward related signal in VMPFC could cause risky behavior, whereas a strong signal in dorsal medial PFC could act as a warning signal to prevent risky behavior. The results from the present study extend these findings and suggest that the relation between activation in these regions and behavior could be related to participants' subjective experience. The VMPFC regions that show a positive correlation with risk-taking were more active when risk averse participants avoided the high-risk option, but showed the opposite pattern for participants who preferred the high-risk gamble on most trials risk; for these participants VMPFC was most active when they chose the high-risk option. Together with the finding that activation in VMPFC regions in all participants is associated with High-Risk choices and with the receipt of gain feedback, these individual differences data stress the need for a better understanding of the role of sub regions of VMPFC and their development (Kringelbach & Rolls, 2004; O'Doherty, 2007; Wallis, 2007).

A question that we could not address in this study but that will be important to examine in future studies is whether monetary rewards hold comparable subjective value for children, adolescents and adults. It could be that the peak in reward related regions in adolescence is observed because the potential monetary reward is more important for

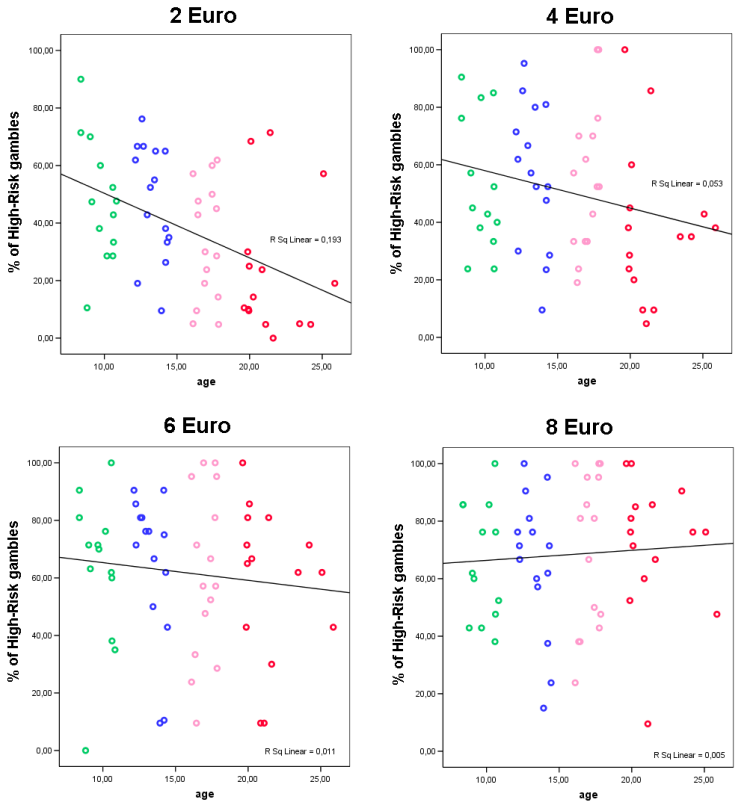
adolescents compared to children and adults. However, the observation that similar brain regions respond to parametric changes in reward value in all age groups and the finding that response time profiles are similar across age groups argue against this possibility. Nonetheless, this will be an important issue to tackle in future experiments.

6.4.4 Conclusion

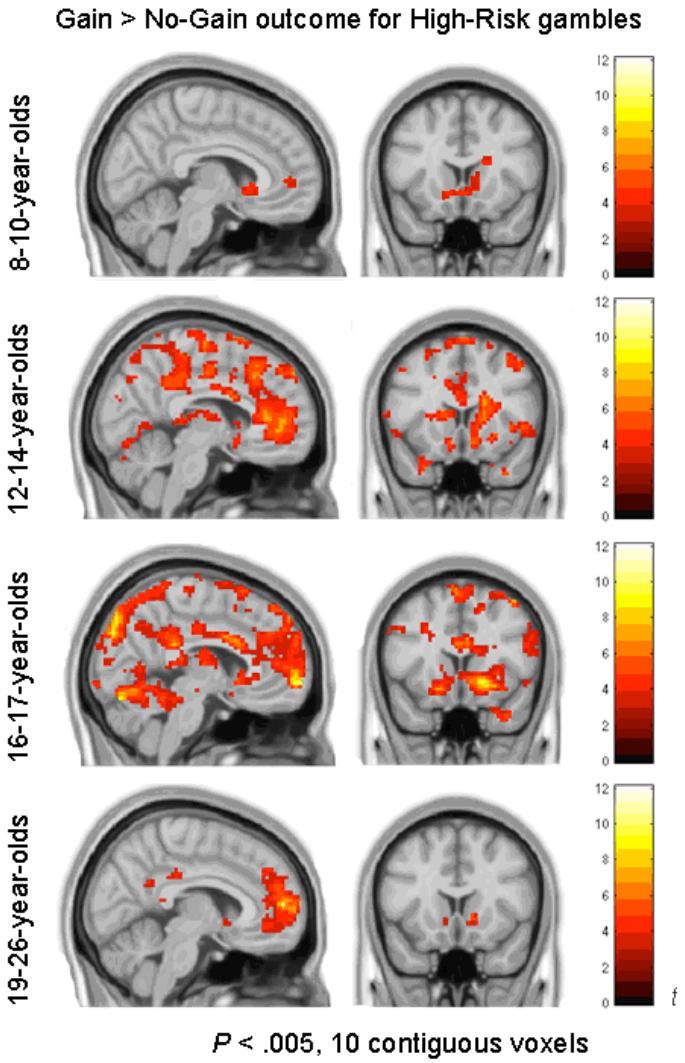
In summary, the current findings demonstrate that brain regions implicated in reward processing and cognitive control in decision-making under risk follow distinct developmental trajectories. Reward related regions show an increased sensitivity to rewards in adolescence and follow an inverted U-shaped developmental pattern, whereas cognitive control related regions mature slowly and follow a linear development. In addition, patterns of activation in dorsal and ventral medial PFC are related to individual differences in risk-taking propensity. These findings support the hypothesis that risky behavior in adolescence follows from an imbalance caused by different developmental trajectories of motivational and regulatory brain circuitry (Casey et al. 2008; Galvan et al. 2006; Steinberg et al. 2008). Importantly, the relative contributions of reward related and control relate regions to decision-making vary with individual differences in risk-taking propensity in all age groups. Future studies should take individual differences into account in order to identify those adolescents who are at risk.



Supplemental Figure 6.1 *Average Reaction times (RT) for High-Risk and Low-Risk gambles shown for each Reward condition (2, 4, 6 and 8 Euro), and Age group (8-10-year-olds, 12-14-year-olds, 16-17-year-olds, and 19-26-year-olds). Error bars depict standard error.*



Supplemental Figure 6.2 *Average % of High-Risk gambles shown for each Reward condition (2, 4, 6 and 8 Euro) and each participant. Data for 8-10-year-olds is presented in green, for 12-14-year-olds in blue, for 16-17-year-olds in pink, and for 19-26-year-olds in red. The Age x Risk correlation was significant in the 2 Euro condition.*



Supplemental Figure 6.3 *Whole-brain results for the contrast of Gain > No-Gain outcomes following High-Risk decisions for the separate age groups [MNI 9, 15, -6]. All images are thresholded at p < .005 uncorrected, 10 contiguous voxels.*

Supplemental Table 6.1 *Activation related to high-risk and low-risk decisions for 8-10, 12-14, 16-17 and 19-26 year olds, at p < .001 uncorrected; with extent threshold of 10 voxels.*

Contrast	Region	MNI coordinates x	y	z	Z-value	Cluster size (voxels)	Cluster corrected
H-R > L-R							
All ages	R Occipital Pole	12	-102	12	4.57	130	$p < .001$
	L Subcallosal cortex	-3	21	-6	4.34	18	$p = .10$
	L Occipital Pole	-12	-105	3	4.34	20	$p = .09$
	L Frontal pole/VMPFC	-6	60	-6	3.96	12	$p = .17$
	L Paracingulate gyrus	-12	51	18	3.62	23	$p = .07$
8-10 yrs	no significant clusters						
12-14 yrs	no significant clusters						
16-17 yrs	L Subcallosal cortex	-3	27	-6	3.85	14	$p = .05$
19-26 yrs	R Anterior cingulate gyrus	12	42	3	3.70	13	$p = .04$
L-R > H-R							
All ages	R Middle frontal gyrus	39	24	36	4.49	54	$p = .009$
	R Superior parietal lobe	24	-42	39	4,15	13	$p = .16$
8-10 yrs	no significant clusters						
12-14 yrs	no significant clusters						
16-17 yrs	L Postcentral gyrus	-33	-33	54	4.73	34	$p = .004$
	R Lateral occipital cortex	18	-72	45	4.23	33	$p = .005$
	L Lateral occipital cortex	-15	-72	45	3.89	13	$p = .06$
	R Middle frontal gyrus	33	0	57	3.88	11	$p = .08$
	L Superior parietal lobe	-21	-48	60	3.44	13	$p = .06$
19-26 yrs	R Lateral occipital cortex	45	-69	33	3.78	12	$p = .05$
	R Middle frontal gyrus	33	30	48	3.65	11	$p = .06$
	R Central opercular cortex	48	-6	6	3.65	11	$p = .06$
	L Postcentral gyrus	-6	-36	69	3.64	16	$p = .03$

Supplemental Table 6.2 *Linear changes in activation for High-Risk > Low-Risk contrast related to reward magnitude across age, at p < .001 uncorrected; with extent threshold of 10 voxels.*

Contrast	Region	MNI coordinates x	y	z	Z-value	Cluster size (voxels)	Cluster corrected
Increase (-3 -1 1 3)							
All ages	R Putamen	24	15	3	4.40	47	$p = .02$
	L Superior temporal gyrus	-57	-39	9	4.16	228	$p < .001$
	L Parahippocampal gyrus	-27	-36	-15	4.12	38	$p = .03$
	L Superior parietal lobe	-24	-48	63	4.03	128	$p < .001$
	R Parietal operculum cortex	39	-30	21	3.96	47	$p = .02$
	L Parahippocampal gyrus	-24	0	-18	3.88	39	$p = .03$
	L Superior parietal lobe	-30	-48	63	3.81	46	$p = .02$
	R Superior temporal gyrus	63	-24	15	3.70	16	$p = .13$
	R Posterior cingulate gyrus	15	-15	39	3.64	12	$p = .19$
	R Superior frontal gyrus	21	-6	63	3.62	17	$p = .12$
	R Amygdala	15	-6	-18	3.59	46	$p = .02$
	R Middle temporal gyrus	60	-54	3	3.56	37	$p = .03$
Decrease (3 1 -1 -3)							
all ages		no significant clusters					

Supplemental Table 6.3 *Changes in activation for High-Risk > Low-Risk contrast related to linear and non-linear age changes, at p < .001 uncorrected; with extent threshold of 10 voxels.*

Contrast	Region	MNI coordinates x	y	z	Z-value	Cluster size (voxels)	Cluster corrected
Increase with age (-3 -1 1 3)							
all rewards		no significant clusters					
2 Euro		no significant clusters					
4, 6, 8 Euro		no significant clusters					
Decrease with age (3 1 -1 -3)							
All rewards							
	R Postcentral gyrus	51	-6	21	4.44	96	$p = .001$
	R Parahippocampal gyrus	21	-15	-24	4.07	19	$p = .09$
	R Anterior cingulate gyrus	12	9	27	3.90	14	$p = .14$
	R Lateral occipital cortex	36	-63	3	3.53	10	$p = .21$
2 Euro		no significant clusters					
4, 6, 8 Euro	R Anterior cingulate gyrus	12	9	27	4.46	19	$p = .08$
	R Central opercular cortex	54	-3	12	4.41	102	$p < .001$
	R Hippocampus	27	-15	-21	3.65	10	$p = .19$
Peak in adolescence (-1 1 1 -1)							
all rewards		no significant clusters					
2 Euro		no significant clusters					
4, 6, 8 Euro	L Subcallosal cortex	-9	27	-12	3.55	10	$p = .19$

Supplemental Table 6.4 *Regions showing a positive or negative correlation with the average % of High-Risk gambles across age, at p < .001 uncorrected; with extent threshold of 10 voxels.*

Contrast	Region	MNI coordinates x	y	z	Z-value	Cluster size (voxels)	Cluster corrected
Positive correlation							
all ages	L Frontal pole/VMPFC	-3	60	-12	5.07	42	$p = .02$
	L Middle temporal gyrus	-57	-9	-18	4.94	127	$p < .001$
	L Inferior frontal gyrus	-54	27	12	4.59	35	$p = .03$
	R Superior temporal gyrus	54	0	-15	4.42	223	$p < .001$
	L Superior temporal gyrus	-66	-36	3	4.30	51	$p = .01$
	L Precuneus cortex	-6	-57	18	3.95	31	$p = .04$
	R Supramarginal gyrus	66	-24	33	3.89	19	$p = .09$
	L Superior frontal gyrus	-21	30	39	3.89	12	$p = .17$
	R Parietal operculum cortex	51	-30	18	3.75	11	$p = .19$
	L Posterior cingulate gyrus	-15	-45	36	3.67	18	$p = .09$
Negative correlation							
all ages	R (Para)cingulate gyrus	6	27	39	6.13	1067	$p < .001$
	R Orbital frontal cortex	30	24	-9	6.0	291	$p < .001$
	L Superior parietal lobe	-30	-60	48	5.24	995	$p < .001$
	L Inferior frontal gyrus	-36	6	27	5.23	231	$p < .001$
	R Posterior cingulate gyrus	6	-24	27	5.11	141	$p < .001$
	L Anterior Insula	-30	18	3	4.88	129	$p < .001$
	R Lateral occipital cortex	30	-63	45	4.63	480	$p < .001$
	R Basal ganglia	12	3	-6	4.45	45	$p = .01$
	L Frontal pole	-30	48	18	4.20	142	$p < .001$
	R Frontal pole	36	51	15	4.16	113	$p < .001$
	R Occipital pole	30	-90	-9	3.85	24	$p = .06$
	R Middle frontal gyrus	33	0	51	3.71	32	$p = .03$
	L Occipital pole	-27	-96	0	3.71	46	$p = .01$
	L Lateral occipital cortex	-36	-78	-15	3.69	14	$p = .14$
	R Middle frontal gyrus	51	15	42	3.64	16	$p = .12$
	R occipital pole	24	-102	0	3.38	12	$p = .17$

Supplemental Table 6.5 *Activation related to Gain feedback following high-risk gambles across age groups and for 8-10, 12-14, 16-17 and 19-26 year olds separately, at p < .001 uncorrected; with extent threshold of 10 voxels.*

Contrast	Region	MNI coordinates x	y	z	Z-value	Cluster size (voxels)	Cluster corrected
Gain > No-Gain							
all ages	L Frontal medial cortex	-3	45	-6	6.27	10993	$p < .001$
	R Nucleus Accumbens	*9*	*15*	*-6*	*6.30*		
	L Nucleus Accumbens	*-9*	*9*	*-9*	*5.73*		
	R Paracingulate gyrus	*6*	*51*	*3*	*6.37*		
	R Inferior temporal gyrus	63	-42	-15	5.71	394	$p < .001$
	L Inferior temporal gyrus	-57	-27	-21	4.94	365	$p < .001$
	L Occipital pole	-27	-102	-6	4.74	65	$p = .005$
	R Putamen	30	-15	-3	3.68	55	$p = .009$
	L Precentral gyrus	-45	-12	36	3.44	17	$p = .12$
	L Postcentral gyrus	-57	-12	36	3.44	15	$p = .14$
8-10 yrs		no significant clusters					
12-14 yrs	L Precentral gyrus	-6	-24	69	4.83	755	$p < .001$
	R Frontal pole	15	48	42	4.80	422	$p < .001$
	L Anterior cingulate gyrus	-9	42	3	4.53	644	$p < .001$
	L Middle frontal gyrus	-39	39	36	4.51	40	$p = .001$
	R Orbital frontal cortex	21	36	-12	4.46	119	$p < .001$
	L Lateral occipital cortex	-45	-66	45	4.41	126	$p < .001$
	L Caudate	-12	12	12	4.33	31	$p = .003$
	R Inferior temporal gyrus	60	-45	-18	4.32	29	$p = .003$
	R Middle frontal gyrus	42	12	48	3.99	28	$p = .004$
	R Supramarginal gyrus	60	-33	45	3.97	15	$p = .03$
	R Middle frontal gyrus	33	33	48	3.96	40	$p = .001$
	L Amygdala	-18	3	-15	3.96	34	$p = .002$
	R Frontal pole	48	48	15	3.95	26	$p = .005$
	L Middle temporal gyrus	-60	-33	-18	3.85	46	$p < .001$
	R Lateral occipital cortex	48	-66	33	3.81	45	$p < .001$
	Superior frontal gyrus	0	12	69	3.79	28	$p = .004$
	R Middle frontal gyrus	45	33	33	3.75	20	$p = .01$
	L Central opercular cortex	-54	3	3	3.74	18	$p = .02$
	L Middle frontal gyrus	-36	9	51	3.69	11	$p = .05$
	L Parahippocampal gyrus	-24	-18	-33	3.66	22	$p = .009$
	L Middle frontal gyrus	-33	18	-30	3.49	14	$p = .03$

	R Anterior insula	42	18	0	3.47	14	$p = .03$
	R Lateral occipital cortex	51	-72	-12	3.45	10	$p = .06$
16-17 yrs	L Posterior cingulate gyrus	-6	-39	27	4.96	1730	$p < .001$
	L Hippocampus	-30	-12	-24	4.82	295	$p < .001$
	R Paracingulate gyrus	15	45	9	4.59	332	$p < .001$
	L Postcentral gyrus	-33	-30	60	4.57	28	$p = .001$
	R Central opercular cortex	57	3	9	4.55	16	$p = .006$
	R Putamen	18	15	-6	4.53	144	$p < .001$
	R Middle frontal gyrus	45	27	36	4.48	26	$p = .001$
	L Lateral occipital cortex	-51	-78	-3	4.45	278	$p < .001$
	R Supramarginal gyrus	33	-42	36	4.34	41	$p < .001$
	L Putamen	-18	18	-12	4.26	68	$p < .001$
	L Frontal pole	-39	48	12	4.26	12	$p = .01$
	L Paracingulate gyrus	-3	39	30	4.23	248	$p < .001$
	R Orbital frontal cortex	36	36	-18	4.16	10	$p = .02$
	L Superior frontal gyrus	-24	30	48	4.12	14	$p = .009$
	L Frontal pole	-24	42	-12	4.08	26	$p = .001$
	R Superior frontal gyrus	15	18	48	3.99	10	$p = .02$
	R Anterior cingulate gyrus	6	6	30	3.97	53	$p < .001$
	L Superior frontal gyrus	-6	18	66	3.95	36	$p < .001$
	R Caudate	12	-12	18	2.87	50	$p < .001$
	R Temporal pole	18	9	-30	3.85	18	$p = .004$
	R Lateral occipital cortex	54	-66	27	3.80	38	$p < .001$
	L Lateral occipital cortex	-51	-75	21	3.65	10	$p = .02$
	R Thalamus	9	-30	12	3.65	26	$p = .001$
	R Occipital pole	12	-96	-6	5.74	13	$p = .01$
	R Lateral occipital cortex	33	-90	-9	5.64	22	$p = .002$
	R Frontal pole	36	45	-3	5.62	33	$p < .001$
	R Supramarginal gyrus	45	-30	36	3.56	20	$p = .002$
	R Angular gyrus	54	-51	45	3.39	39	$p < .001$
19-26 yrs	R Frontal pole	9	63	6	4.85	356	$p < .001$
	L Frontal pole	-39	42	-3	4.72	62	$p < .001$
	L Supramarginal gyrus	-57	-36	48	4.20	11	$p = .01$
	R Lateral occipital cortex	51	-66	27	3.80	23	$p = .001$
	L Lateral occipital cortex	-39	-63	24	3.79	37	$p < .001$
	L Precuneus cortex	-15	-63	39	3.74	11	$p = .01$
	L Lateral occipital cortex	-33	-81	42	3.70	22	$p = .001$

No-Gain > Gain

all ages no significant clusters

8-10 yrs no significant clusters

12-14 yrs	no significant clusters
16-17 yrs	no significant clusters
19-26 yrs	no significant clusters

7.

Developmental trends for object and spatial working memory: A psychophysiological analysis

This study examined developmental trends in object and spatial working memory (WM) using heart rate (HR) to provide an index of covert cognitive processes. Participants in four age groups (6-7, 9-10, 11-12, 18-26, n = 20 each) performed object and spatial WM tasks, in which each trial was followed by feedback. Spatial WM task performance reached adult levels before object WM task performance. The differential developmental trends for object and spatial WM found in this study are taken to suggest that these WM components are separable. Negative performance feedback elicited HR slowing that was more pronounced for adults than for children. The development of performance monitoring as indexed by covert HR slowing following performance feedback contributes to WM performance.

7.1 Introduction

Working memory (WM) comprises those functional components of cognition that allow humans to comprehend and mentally represent their immediate environment, to retain information about their immediate past experience, to support the acquisition of new knowledge, to solve problems, and to formulate, relate, and act on current goals (Baddeley & Logie, 1999). Therefore, WM is a key component of human cognition. The developmental literature has consistently shown that children's ability to maintain and manipulate information in WM develops slowly, and does not reach mature levels until late childhood (Casey, Giedd & Thomas, 2000; Diamond, 2002; Gathercole, Pickering, Ambridge & Wearing, 2004; Hamilton, Coates & Heffernan, 2003; Hitch, 2002; Logie & Pearson, 1997; Pickering, 2001; Pickering, Gathercole, Hall & Lloyd, 2001). WM is an important contributor to many abilities that are acquired during the school-age period, such as reading and mathematics (Cowan et al., 2003; Gathercole, 2004; Hitch, Towse & Hutton, 2001) and it is often conceptualized as the driving force behind cognitive development (Case, 1992; Pascual-Leone, 1995, Kail, 1990).

One of the most generally accepted conceptualizations of WM come from a model developed by Baddeley and Hitch (Baddeley & Hitch, 1974; Baddeley, 1992a; 1992b). This model suggests that WM is a construct consisting of multiple specialized components of cognition, including a supervisory system (the "central executive") and specialized temporary memory systems; a phonologically based store (the phonological loop) and a visuospatial store (the visuospatial sketchpad). The central executive is involved in the control and regulation of the WM system. It is considered to perform various executive functions, such as coordinating the two temporary memory systems, focusing and switching attention, and activating representations within long-term memory. Despite the fact that the unitary structure of the central executive has been called into question (e.g., Alloway, Gathercole & Pickering, 2006 Engle, Tuholski, Laughlin, & Conway, 1999; Kane et al., 2004; Bayliss, Jarrold, Gunn, & Baddeley, 2003; Wagner, Bunge & Badre, 2004, see also: Friedman & Miyake, 2000; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001), WM is generally agreed to consist of multiple specialized temporary memory systems.

Many studies have focused on phonological short-term memory in adults (Baddeley, 1992a, 1992b; Smith & Jonides, 1997) and in children (Alloway & Gathercole, 2005; Baddeley, Gathercole & Papagno, 1998; Cowan, 2002; Gathercole, Pickering, Ambridge & Wearing, 2004; Gathercole & Hitch, 1993; Hitch, 2002). Visuospatial short-term memory has received less attention and is less well understood than phonological WM. Initially, visuospatial WM was assumed to be a unitary system for setting up and manipulating visuospatial images as well as storing short-term visuospatial information (Baddeley & Hitch, 1974; Baddeley, 1992a, 1992b). Numerous studies however, have shown a double dissociation between tasks for object and spatial WM suggesting empirical evidence for the existence of separate subcomponents within the visuospatial sketchpad (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999; Hecker & Mapperson, 1997; Klauer & Zhao, 2004; Logie, 1995; Mecklinger & Pfeiffer, 1996; Smith et al, 1995; Belger et al., 1998; Nystrom et al., 2000). Animal and human neuroimaging studies, for example, have shown that spatial and object memory are related to activation in different brain regions, the dorsal and ventral prefrontal cortex, respectively (Courtney, Ungerleider, Keil & Haxby, 1996; Wilson, O'Scalaidhe, Goldman-Rakic, 1993).

Recent studies that have attempted to examine the development of separate subcomponents for object and spatial WM in a single design (Hamilton, Coates, & Heffernan, 2003; Logie & Pearson, 1997; Pickering, Gathercole, Hall & Lloyd, 2001) suggest that developmental trajectories for object and spatial WM components can be dissociated through use of the *developmental fractionation technique* (Hitch, 1990). According to this technique, age-related changes in object WM have been observed to follow a slower trajectory than age-related changes in spatial WM. However, Hamilton, Coates and Heffernan (2003) argued that these findings should be interpreted with caution given their observation that WM performance is influenced by age-related changes in the speed of information processing and by executive control functions. Importantly, the relative contribution of these factors to WM performance was found to differ between age groups complicating the assessment of developmental trends in WM. Similarly, in the context of the multi-component WM model (Baddeley & Hitch, 1974) we should take into account to what extent tasks used to assess object and spatial

WM components tap control functions exercised by the central executive (Hitch, Towse & Hutton, 2001; Klauer & Zhao, 2004). Executive control functions may well continue to develop into adolescence (Diamond, 2002; Huizinga, Dolan & Van der Molen, 2006; Luna, Garver, Urban, Lazar & Sweeney, 2004; Stuss 1992; Welsh, 2002), complicating the interpretation of the results of studies of WM development.

The primary goal of the present study was to examine developmental trends in object and spatial WM while keeping procedural differences between object and spatial WM tasks minimal. Participants were presented with series of stimuli ranging between 4 and 8 items. They were required to respond to the stimulus using one button when the stimulus was new (object task) or presented in a new location (spatial task), and another button when the stimulus had been presented previously in the series (object task) or when it occupied a location that it had occupied previously (spatial task). The participants also performed two control tasks in which the previously presented stimuli (object task) or locations (spatial task) were cued. Memory demands were allegedly absent in the control tasks, therefore response speed and accuracy were assumed not to discriminate between different series lengths, and between object and spatial WM control tasks. In addition, a reaction time task as a measures of basic performance speed and the Random Number Generation (RNG) task, a task that has been demonstrated in the past to provide a reliable indicator of executive control function (Baddeley, Emslie, Kolodny & Duncan, 1998; Miyake et al., 2000; Towse & Neil, 1998).were included to allow for an assessment of their potential contribution to developmental trends in object and spatial WM

A secondary goal of the present study was to examine developmental trends in object and spatial WM vis-à-vis the recordings of the participants' heart rate (HR) during task performance. There is a large body of research showing a bi-directional relation between HR and information processing demands. HR decelerates during the deployment of attention in the service of detecting potentially relevant information, whereas processing and transforming that information is associated with HR speeding (Lacey & Lacey, 1974; for a review: Van der Molen, Somsen & Orlebeke, 1985). In previous work, HR has been observed to

slow when participants anticipate a target stimulus embedded in a series of non-target stimuli, with more slowing when the number of non-target stimuli preceding the target stimulus increased (Van der Molen, Somsen & Jennings, 2000). This anticipatory slowing of HR became more pronounced with advancing age from middle childhood into adolescence and adulthood (Van der Molen, Somsen & Jennings, 2000). In related studies, focusing on the processing of feedback stimuli, HR was found to decelerate in anticipation of performance feedback with added deceleration when the information provided by the feedback was negative (Crone et al., 2003). The cardiac changes associated with feedback processing were less pronounced during childhood compared to adolescent and adult participants (Crone, Jennings & Van der Molen, 2004). Finally, it has been shown that mnemonic task demands induce HR speeding, the more so when the task demands on memory processing increase (e.g., Backs & Seljos, 1994; for a review see Jennings, 1986).

The pattern of findings that emerged from the HR literature on information processing provides the context for a set of specific predictions regarding the relation between object and spatial WM on the one hand and cardiac changes on the other. First, preparing for the WM target stimulus is predicted to induce an anticipatory HR deceleration that returns to baseline at the time of the initiation of the response (e.g., Somsen, Van der Molen, Jennings & Orlebeke, 1985). Second, increasing demands on WM should elicit an acceleratory HR trend reducing the peak of anticipatory deceleration (e.g., Backs & Seljos, 1994). Assuming that WM demands are similar for object and spatial WM tasks, anticipatory HR changes should not differentiate between tasks. Third, the anticipation of performance feedback was assumed to induce added deceleration that is larger for negative feedback compared to positive feedback (e.g., Crone et al., 2003). The cardiac changes associated with feedback processing were predicted to be smaller in children compared to adults (Crone, Jennings & Van der Molen. 2004; Van der Molen, Somsen & Jennings, 2000). Finally, it was assumed that the magnitude of the cardiac changes associated with feedback processing is proportional to the ability to detect that an error has been made in response to the target stimulus. This ability should decrease with increasing WM load and should be less pronounced for children compared to adults. In sum, this study aimed at investigating developmental trends in object and spatial WM using HR changes as

converging measures of processing demands on WM and performance monitoring.

7.2 Method

7.2.1 Participants

Three groups of children and one group of young adults participated in the study; twenty 6-7 year-olds (11 girls, M = 6.6, SE = .68), twenty 9-10 year-olds (11 girls, M = 9.7, SE = .72), twenty 11-12 year-olds (11 girls, M = 11.9, SE = .70) and twenty 18-26 year-olds (10 females, M = 21.9, SE = 2.09). The young adults were students at the University of Amsterdam who received course credit for participating. The children were recruited through a local school, and were selected with the help of their teachers and with their parents' consent. Children who participated in the study had average or above average IQ according to teacher reports. Participants with learning disorders, behavioral disorders or a history of neurological impairments were excluded from the study. No detailed information regarding parental income, parental education level, or family size of the participants was collected. However, participants were mostly Caucasian, and tended to come from middle class families.

7.2.2 Experimental Tasks

Stimulus Displays

For the object tasks, two displays were presented on each trial, a stimulus display and an outcome display. The object WM task stimulus display consisted of a square box at the center of the screen in which different abstract symbols were presented in sequential order. Abstract figures (www.cog.brown.edu/~tarr/stimuli.html#pw) were used to minimize the possibility that participants would use verbal strategies. In the spatial WM task 4, 6, or 8 square boxes were presented in a vertical row at the center of the screen. On each trial, a happy face was presented on one of the square boxes. Participants were told that the square boxes in both the object task and the spatial task each contained a reward, and were instructed to collect as many rewards as possible. To this end, they were required to press one of two keys ('Z' or '/') with their left or right index finger respectively. The keys corresponded to the options 'open the box' and 'do not open the box'. The assignment of

keys was counterbalanced across participants and kept fixed across the experiment. Participants were not instructed to respond as fast as possible. A representation of the stimulus displays used in the object and spatial WM tasks and an example of a trial are presented in Figure 7.1. Participants were instructed that in the object WM task, a box should be opened every time a *new figure* was presented, but should be kept closed when an earlier displayed figure was presented. In the spatial WM task participants were instructed to open a box every time the happy face was presented in a *new location*, and not when it appeared in one of the locations it was presented in before.

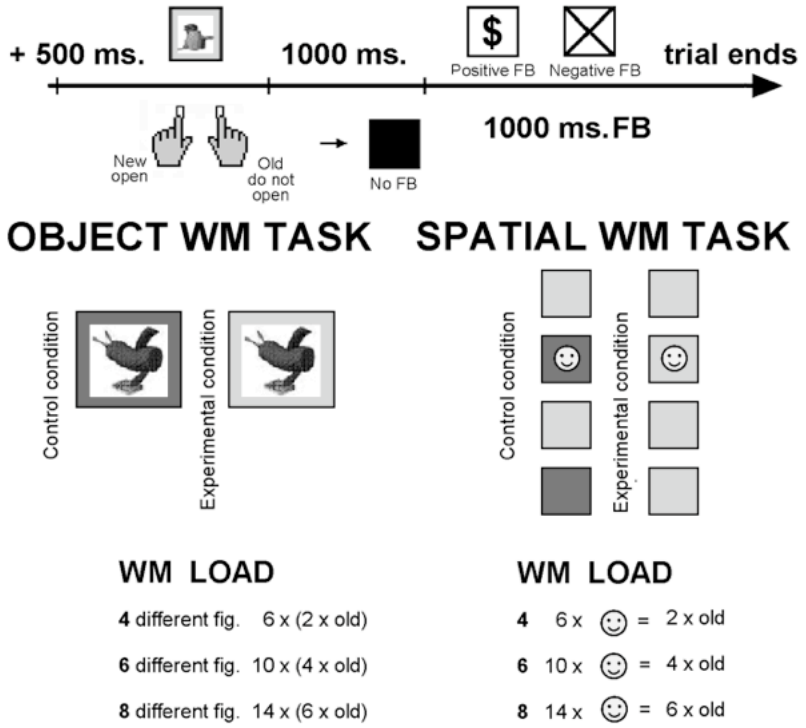


Figure 7.1 *Object WM task trial with examples of positive ($), negative (x) and non-informative (■) feedback displays. The bottom half of the figure shows the task design and stimulus displays for the experimental and control conditions of the WM tasks. See text for details about stimulus presentation.*

This manipulation required participants to keep track of the figures that were already seen within the sequence and the locations that had already been occupied. Upon pressing one of the keys, the stimulus display was replaced by the outcome display showing a square

containing a '$' sign, indicating that the box was opened correctly, or an 'X' sign, indicating that the box was opened incorrectly. If the participant decided not to open the box, it turned black irrespective of the accuracy of the participant's decision.

The task consisted of two separate conditions. In the experimental condition, the edge of the square box was always green in the object WM task, and the square boxes were always green in the spatial WM task, therefore the participants needed to remember if a figure had been seen before, or if a happy face had previously appeared in a location. In the control condition, all performance requirements were the same, except that in this condition in the object task the edge of the square box turned red when a previously seen figure was presented, and in the spatial task the square box in which the happy face appeared turned red when it was a location where it had appeared before. The order of experimental and control conditions was counterbalanced across participants. The presentation time of the target stimulus was response-terminated. A response resulted in a 1000 ms blank screen, followed by a 1000 ms outcome display. The inter-trial interval varied between 500, 1000, 1500 or 2000 ms.

Task Design.

In each block, three series of trials consisting of 4, 6, or 8 different abstract symbols or spatial locations were presented. Thus, both the object and spatial WM tasks consisted of Load 4, 6, and 8 trials. Symbols and locations were presented 6, 10, or 14 times, requiring participants to open the box 4, 6 and 8 times and keeping it closed 2, 4 and 6 times, respectively (see Figure 7.1). Which stimuli were repeated was pseudo-randomized to ensure that two consecutive trials were never identical and that the stimulus associated with the final trial in a series had not been previously seen. Participants had to keep stimuli active in memory throughout the series. During both WM tasks, the Load 4, 6, and 8 trial series were presented 4 times in the control condition and 4 times in the experimental condition. Consequently a total of 24 Load 4 trials, 40 Load 6 trials, and 56 Load 8 trials were presented in both the experimental and control condition, resulting in 120 trials for the control condition and 120 trials for the experimental condition in total. To familiarize participants with the stimuli and procedure, they received a block of practice trials consisting of two series of 6 and 8 experimental and control trials at the beginning of each task.

Speed of Processing (SP)Task

The SP task was based on a 2-choice reaction time task adopted from Van den Wildenberg (2003). In the SP task, an arrow was presented in the center of the screen, pointing to the left or to the right. Participants had to respond to this arrow as quickly and accurately as possible by pressing the 'Z' or '/' key with their left or right index finger, corresponding to the direction of the arrow. The response-to-stimulus interval was set at 1000 ms. Participants received a block of 15 practice trials at the beginning of the task. The task consisted of a series of 75 trials.

Random Number Generation (RNG) Task

The RNG task was a computer version of the RNG task (Huizinga, Dolan & Van der Molen, 2006) developed by Towse & Neil (1998). Participants were required to generate numbers randomly by pressing keys, labeled 1 to 10, on a computer keyboard. A brightly colored star was shown for 1000 ms on each trial, after which it was replaced by a question mark indicating that participants should respond as fast as possible. The response-to-stimulus interval was set at 1000 ms. Participants received a block of 15 practice trials at the beginning of the task. The RNG task consisted of a block of 75 trials.

Exit Interview

Upon completing the experiment, all participants were asked if they had used any particular strategy when performing the WM tasks. Special attention was given to any kind of verbal strategies participants might have used. These strategies were probed by questions like: "How did you remember which box you should open or how did you remember which object was old or new?" All answers were quantified, using two categories. Participants who reported they were "naming the abstract figures" were coded as having used a verbal strategy. Participants reporting, for example, to have "just looked at the pictures" were coded as using a non-verbal strategy.

Psychophysiological Measures.

During the WM tasks, the electrocardiogram (ECG) and respiration were continuously recorded. The ECG was recorded from three electrodes, attached via the modified lead-2 placement. Respiration was recorded through a sensor situated across the abdomen. The signals were sampled and recorded by a computer at a rate of 400 Hz. The

recorded Inter-Beat Intervals (IBIs) were screened for physiologically impossible readings and artifacts. These were corrected by adjusting specific parameters in the program that extracted the IBIs from the digitized ECGs. The respiration signal was used only to eliminate heart rate changes associated with gross respiratory changes (Jennings et al., 1981).

Procedure.
All participants were tested individually in a quiet laboratory or classroom. All participants completed all tasks. Each session began with attaching the physiological equipment and ended with the exit-interview. The tasks were presented in two possible orders: RNG, Spatial WM, Object WM and RT or vice versa. Stimuli were presented in color against a white background on a 15-inch computer screen placed at a distance of 70 centimeters from the participant. Preceding each task participants were given written instructions, which were shown on the screen. To make sure that even the youngest children understood the instructions, these were also read to the participants and care was taken that all participants understood the instructions after practice. The two WM tasks took approximately 25 minutes each to complete. The other tasks lasted approximately 5 minutes each. There were short breaks between all tasks, and children were given a drink and a cookie halfway through the experiment. Including instructions and breaks, participants spent approximately 90 minutes in the laboratory or classroom.

7.3 Results

Results will be presented in two major sections. The performance results will be presented first, followed by the presentation of the HR findings.

7.3.1 Behavioral Data

The performance of participants was examined by computing accuracy and median reaction times. The data were then submitted to repeated measures ANOVAs with Age Group (4), as a between-subjects factor and Task (object/spatial) and Condition (experimental/control), and Load (4, 6 or 8) as within-subjects factors.

Response Accuracy on the WM Tasks

The accuracy scores for each age group are presented in Figure 7.2. Main effects for Age Group, Task, Condition and Load were significant (all p's < .001, all η_p^2 > .521) and these effects were qualified by a significant four-way interaction between Age Group, Load, Condition and Task, F (6, 152) = 8.04, p < .001, η_p^2 = .241. The four-way interaction was followed up by separate ANOVAs for the experimental and control conditions. The ANOVA on the data from the control condition did not result in any significant effects, p's > .05. In contrast, the ANOVA for the experimental condition yielded a Load x Task Type interaction, F (2, 152) = 16.34, p < .001, η_p^2 = .177, that showed a larger increase in the percentage of errors with an increase in WM load for the spatial WM task (15%) than for the object WM task (7%). This interaction was qualified by a three way-interaction between Age Group, Load and Task Type, F (6, 152) = 9.34, p < .05, η_p^2 = .269. Separate analyses revealed a significant interaction between Age Group and task demands for the spatial WM task, F (6, 152) = 13.28, p < .001, η_p^2 = .344. Comparisons between age groups indicated that the effect of spatial WM load was significantly larger in the in 6-7 year olds compared to the 9-10 year olds, F(2, 76) = 4.63 p < .05, η_p^2 = .109, the 11-12 year olds, F (2, 76) = 22.16 p < .001, η_p^2 = .368, and the 18-26 year olds, F(2, 76) = 29.78 p < .001, η_p^2 = .439. The 9-10 year olds showed a larger effect of increasing WM load than the 11-12 year olds, F (2, 76) = 6.74, p < .01, η_p^2 = .151, and the 18-26 year olds, F(2, 76) = 12.24, p < .001, η_p^2 = .244. Finally, the 11-12 year olds and 18-26 year olds did not differ significantly from each other, p = .28, η_p^2 = .033.

Similar analyses done on the performance data generated by the Object task revealed only a main effect of Age Group, p < .001, η_p^2 = .463, but no Load x Group interaction, p > .05, η_p^2 = .067. Thus, in the Object task, the effect of WM load did not differ between age groups. However, a repeated measures ANOVA on the Object task data with Age Group (4), as a between-subjects factor and Condition (experimental/control), and Load (4, 6 or 8) as within-subjects factors, did result in a Condition x Age Group interaction, F (3, 76) = 12.09, p < .001, η_p^2 = .323. The decrease in accuracy in the experimental condition, relative to the control condition, was smaller in older participants. Comparisons between age groups showed that the increase in the percentage of errors as a function of WM load was significantly larger for 6-7 year olds (22%) than for 9-10 year olds (15%), F (1, 38) = 9.80 p < .01, η_p^2 = /205, 11-12 year olds (16%), F (1, 38) = 7.71 p < .

01, η_p^2 = .169, and 18-25 year olds (8%), $F(1, 38) = 42.20$ $p < .001$, η_p^2 = .526. The 9-10 year olds did not differ from the 11-12 year olds, $p = .98$, η_p^2 = .000, but the 9-10 year olds and the 11-12 year olds performed significantly worse than the 18-25 year olds (F (1, 38) = 11.05, $p < .01$, η_p^2 = .225, and F (1, 38) = 8.53, $p < .001$, η_p^2 = .183, respectively). Thus, spatial WM performance, as indexed by accuracy, reached adult levels earlier (at age 11-12) than object WM performance (beyond age 11-12).

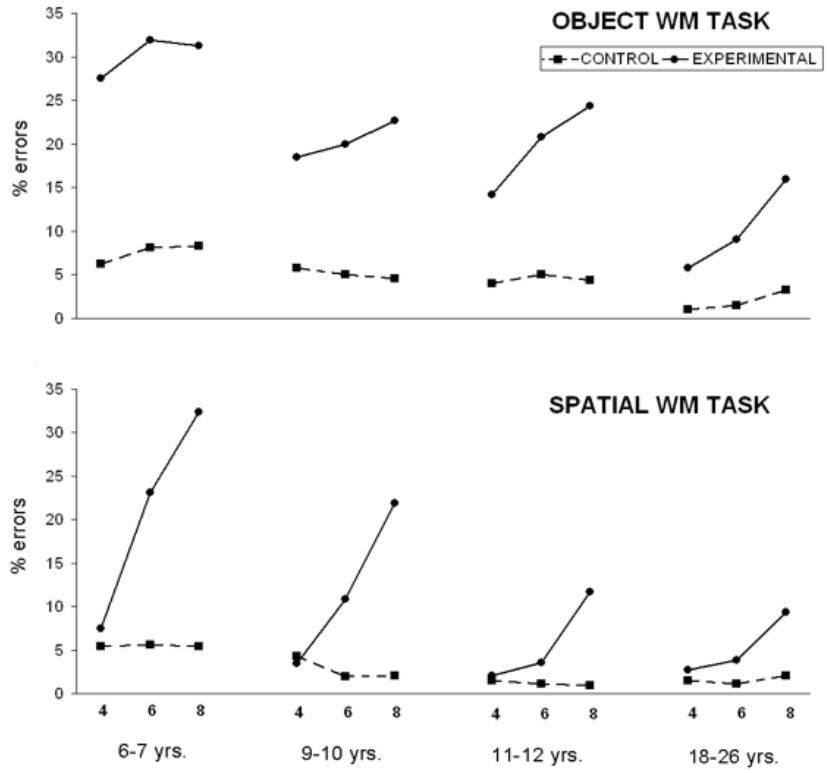


Figure 7.2 *Average percentage of errors in the experimental and control condition as a function of increasing WM load for each age group and both WM tasks separately. Age differences are observed in the experimental condition for both the spatial and object WM tasks.*

Response Speed on the WM Tasks

Median reaction times (RT) for each Age Group, WM task, Condition, and WM load are presented in Table 1. A similar ANOVA as for accuracy was performed on the speed of responding and the RT results generally parallel the accuracy results. Again, all main effects were

Table 7.1

Median Reaction Time for Each Age Group, Task, Condition, and WM Load

	Spatial						Object					
	Control			Experimental			Control			Experimental		
Task condition WM load	4	6	8	4	6	8	4	6	8	4	6	8
Age group 6- to 7-year-olds ($n = 20$)												
RT	1,256	1,210	1,253	1,252	1,533	1,488	1,473	1,456	1,438	1,861	1,853	1,901
SE	73.7	53.2	52.6	58.2	77.5	72.8	74.1	67	69.6	106.7	91.6	105.2
9- to 10-year-olds ($n = 20$)												
RT	793	806	823	827	887	995	1,142	1,069	1,141	1,326	1,341	1,375
SE	73.7	53.2	52.6	58.2	77.5	72.8	74.1	67	69.6	106.7	91.6	105.2
11- to 12-year-olds ($n = 20$)												
RT	690	722	726	734	810	956	943	901	921	1,113	1,189	1,150
SE	73.7	53.2	52.6	58.2	77.5	72.8	74.1	67	69.6	106.7	91.6	105.2
18- to 26-year-olds ($n = 20$)												
RT	548	564	572	585	651	776	743	704	709	985	1,050	1,027
SE	73.7	53.2	52.6	58.2	77.5	72.8	74.1	67	69.6	106.7	91.61	105.2

Note. RT = reaction time in ms; WM = working memory.

significant (all p's <.001, all η_p^2 > .121). These effects were qualified by a four-way interaction between Age Group, Load, Condition and Task Type, F (6, 152) =3.50, p < .01, η_p^2 = .121. A follow-up ANOVA on the RTs that emerged from the control task did not result in significant effects (all p's > .05, all η_p^2 < .556). Subsequent analyses for the experimental condition resulted in a significant Task x Load x Group interaction, F (6, 152) = 2.85, p < .05, η_p^2 = .101. The analyses done on the data from the Spatial WM task yielded a significant Load x Group interaction, F (6, 152) = 3.19, p < .01, η_p^2 = .112. This interaction revealed that the effect of an increase in WM load in 6-7 year olds differed significantly from the effect in 9-10 year olds, F(2, 76) = 3.82, p < .05, η_p^2 = .091, in the 11-12 year olds, F (2, 76) = 4.02, p < .05, η_p^2 = .096, and in the 18-26 year olds F(2, 76) = 4.30, p < .05, η_p^2 = .102. RT increased with WM load in all age groups but reached a plateau for the 6-7 year olds when WM load increased from 6 to 8 locations; M = 1533, SE = 138.1 and M = 1488, SE = 114.7, respectively.

A similar analysis on the data from the Object WM task yielded only a main effect of Age Group, F (3, 76) = 15.60, p < .001, η_p^2 = .381. Post hoc Tukey tests revealed that the 6-7 year olds responded slower (M = 1872, SE = 94.8) than the 9-10 year olds (M = 1347, SE = 94.8), the 11-12 year olds (M = 1151, SE = 94.8), and the 18-25 year olds (M = 1021, SE = 94.8). Load did not alter the preceding effects. In broad outline, these results are consistent with the accuracy results reported previously. That is, performance reached an adult level for the spatial WM task earlier than for the object WM task.

Response Speed on the SP Task.

Performance on the SP task was evaluated by computing accuracy and median RT for each participant. The SP data were then submitted to a one way-ANOVA with Group (4) as between-subjects factor. The ANOVA for accuracy showed a main effect of Group, F (3, 76) = 18.56, P < .001. Post hoc Tukey tests revealed that 6-7 year olds were less accurate (M = 15.9 %, SE = 8.2) than the 9-10 year olds (M = 7.7 %, SE = 6.1), the 11-12 year olds (M = 3.6 %, SE = 3.0) and the 18-26 year olds (M = 3.9 %, SE = 5.4). The three oldest groups did not differ significantly from each other. The ANOVA done on the speed of responding showed a main effect of Group as well, F (3, 76) = 36.20, p < .001. Post hoc Tukey tests indicated that the 6-7 year olds (M = 588.67, SE = 91.4) responded slower than the 9-10 year olds (M =

511.66, *SE* = 86.3), the 11-12 year olds (*M* = 457.71, *SE* = 54) and the 18-26 year olds (*M* = 362.37, *SE* = 35.8). Mean SP did not differ between the 9-10 year olds and 11-12 year olds, but the oldest group responded faster than all three younger groups (all *p's* <.05). Finally, correlations between speed and accuracy were not significant.

Random Number Generation (RNG).

Performance on the RNG task was assessed using Towse and Neil's (1998) RgCalc program which produces several different indices of "randomness". The Random Number Generation (RNG) index was used for our purposes. The RNG index provides the frequency of response pairs, and this frequency value may vary between 0 (fully random) and 1 (fully predictable). The RNG frequency index was submitted to a one way ANOVA with Age Group (4), as a between-subjects factor, and RNG, as within-subjects factor. The ANOVA failed to reveal significant differences between age groups, $p = .46$.

SP and RNG Predictors.

SP scores were submitted as covariates in an ANCOVA on the WM data with Age Group (4), as a between-subjects factor, and Task (object, spatial), Condition (experimental, control) and Load (4, 6 or 8), as within-subjects factors. Importantly, the previously observed four-way interaction between Task x Load x Condition x Group remained significant, $F(6, 150) = 3.75$, $p < .01$, $\eta_p^2 = .131$, when SP was added as covariate. The ANCOVA revealed a significant interaction between SP and Condition, $F(1, 75) = 6.93$, $p < .01$, $\eta_p^2 = .085$. An additional correlation analysis was performed to examine this interaction. The correlation analysis showed that the difference in accuracy between the experimental and control condition correlated significantly with SP, $r = .63$, $n = 80$, $p < .001$. The partial correlation, corrected for age group, was also significant, $r = .29$, $n = 77$, $p < .01$. This positive relation indicated that accuracy on WM tasks increased as participants responded faster on the SP task. This association was consistent across all age groups. RNG scores were submitted as covariates in a similar ANCOVA on the WM data. Again, the previously observed four-way interaction between Task x Load x Condition x Group remained significant, $F(6, 150) = 8.14$, $p < .001$, $\eta_p^2 = .246$. However, correlation analyses for difference scores between the experimental and control

conditions did not show a significant correlation with RNG for the object ($p >$. 05), and spatial ($p >$. 05) WM tasks.

Verbal Strategies.

The exit interview showed that several participants used a verbal strategy in the WM tasks. For the Spatial WM task 10% of 6-7 year olds, 15% of 9-10 year olds, 35% of 11-12 year olds and 20% of 18-26 year olds reported to have used a verbal strategy. However, for the object task respectively 10%, 35%, 55% and 100% of participants reported using a verbal strategy. To determine whether verbal strategy use influenced WM task performance, the data were submitted to repeated measures ANOVAs with Age Group (2) and Strategy (verbal, non-verbal), as between-subjects factors, and Condition (experimental, control) and Load (4, 6 or 8), as within-subjects factors. The data of the 6-7 year olds and 18-26 year olds were not included in this analysis, as only 10% of participants in the youngest group and all participants in the oldest group indicated that they used a naming strategy when performing the object WM task. Consequently, the Age Group factor had only two levels (9-10-years vs. 11-12-years). The ANOVAs were performed on the data of each WM task, separately. The ANOVA done on the Spatial WM task data yielded a significant Condition by Strategy interaction, F (1, 36) = 6.43, $p < .05$, $\eta_p^2 = .152$. Post hoc analyses showed that participants who used a verbal strategy were more accurate in the experimental condition than participants who did not (M = 9.77, SE = .95 vs. M = 5.57, SE = 1.78, respectively), F (1, 36) = 4.33, $p <$. 05, $\eta_p^2 = .107$, but not in the control condition, $p > .05$, $\eta_p^2 = .010$. Likewise, the ANOVA done on the Object WM task data showed that participants who used a verbal strategy were more accurate than participants who did not use a verbal strategy when performing the experimental task (M = 23.86, SE = 1.56 vs. M = 16.35, SE = 1.74) , F (1, 36) = 10.30, $p < .01$. $\eta_p^2 = .223$. Age group did not alter any of these effects.

7.3.2 Heart Rate Changes

The HR analyses are presented in two separate sections. The first set of analyses focused on the HR changes associated with the processing of the target stimulus and the second set of analyses focused on cardiac responses associated with the processing of the feedback stimulus. *Cardiac Response Associated With Target Processing*.

The cardiac response associated with the processing of the target stimulus in the control and experimental condition for the object and spatial WM tasks is presented in Figure 7.3. In this figure, the cardiac response is plotted in terms of inter-beat intervals (IBIs). Thus, a lengthening of IBI indicates a slowing of HR.

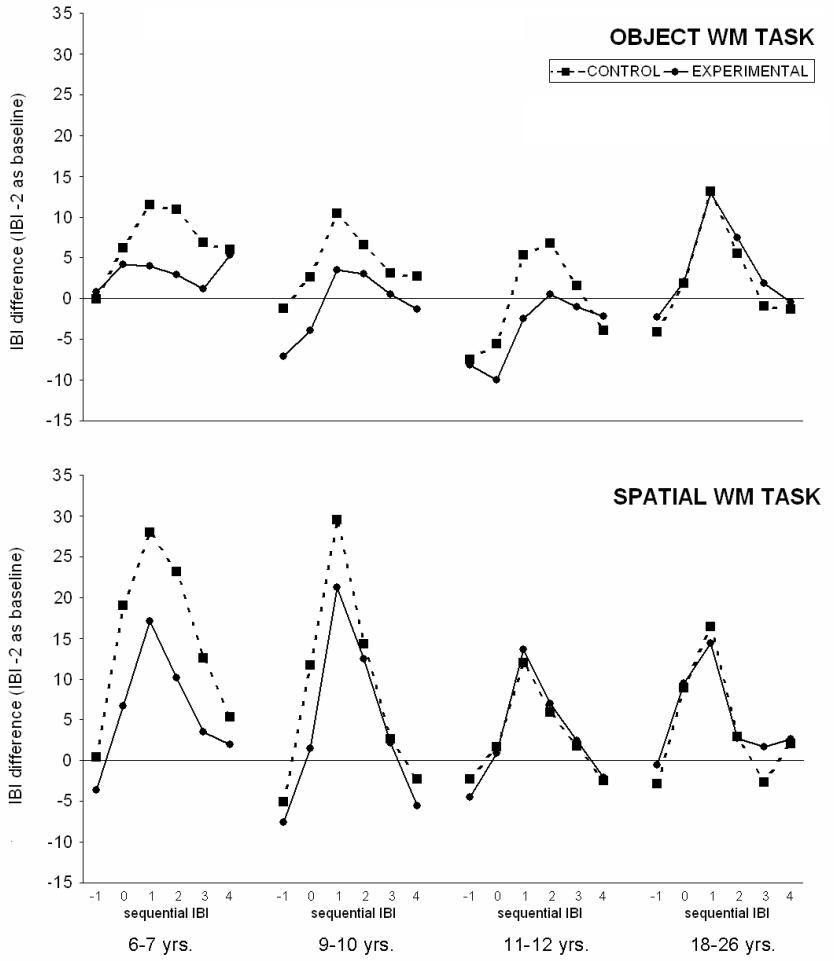


Figure 7.3 *Six IBIs are plotted around the presentation of the stimulus (IBI 0). Average IBI length is plotted for the control and experimental condition for both WM tasks and for each age group separately. Heart rate slows during stimulus presentation, but the relative slowing is reduced in the object WM task.*

The cardiac response is plotted around the presentation of the target

stimulus. That is, the target stimulus occurred during the IBI indicated as IBI-0 in the figure. The preceding IBI (IBI-1) and subsequent IBI's (IBI1, IBI2, IBI3 and IBI4) are plotted around the IBI of the target stimulus (IBI0). The IBI response is plotted relative to a pre-target stimulus baseline (IBI-2; i.e., two IBIs preceding the IBI of the target stimulus).

The plots presented in Figure 7.3 show the cardiac response that is typically observed when participants prepare for a significant stimulus. That is, an IBI lengthening (i.e., cardiac slowing) preceding the stimulus and a return to baseline (acceleratory recovery) upon the initiation of the response to the stimulus. In addition, it can be seen that cardiac slowing is considerably less pronounced in the object WM task compared to the spatial WM task. Quite unexpectedly, the plots presented in Figure 7.3 show that the difference between object and spatial tasks occurred both for the experimental and control conditions. Finally, Figure 7.4 shows that WM load exerted only minimal effects in the object WM task in contrast to a pronounced effect that the highest WM load has in the spatial WM task. The visual impressions created by Figure 7.3 and 7.4 were verified statistically by a repeated measures ANOVA done on IBI1, with Group (4), as a between subjects factor, and Task (object, spatial), Condition (experimental, control), and Load (4, 6, or 8), as within subjects factors. The analysis focuses on the IBI following the presentation of the stimulus (IBI 1), since previous studies showed that IBI 1 shows the most pronounced effects of the experimental manipulation for both stimulus processing (Somsen et al., 1985) and feedback processing (Crone, Jennings & Van der Molen, 2004; Crone et al., 2003).

The ANOVA yielded a significant main effect of Task, F (1, 76) = 37.87, $p < .001$, $\eta_p^2 = .333$, that was qualified by an interaction between Task and Load, F (2, 152) = 4.46, $p < .05$, $\eta_p^2 = .055$. This interaction was not altered by the effect of Condition, $p > .05$, $\eta_p^2 = .028$. Follow-up analyses performed on the data of the experimental condition revealed a significant Task by Load interaction, F (2, 152) = 6.37, $p < .001$, $\eta_p^2 = .077$. Load altered the cardiac response in the spatial WM task, F (2, 152) = 11.40, $p < .001$, $\eta_p^2 = .130$, but did not in the object WM task, $p > .10$, $\eta_p^2 = .000$ (see Figure 7.4). Importantly, Age Group effects were absent, with the exception of an interaction between Condition and Age Group that approached significance, F (3, 76) =

2.29, $p = .085$, $\eta_p^2 = .083$. This interaction is plotted in Figure 7.3. This figure shows that the difference between experimental and control conditions is much more pronounced in the child groups compared to adult participants. A post-hoc analysis, collapsing data across the two youngest groups and the two oldest groups, indicated that the IBI shortening (i.e., cardiac speeding) induced by the mnemonic task demands was more pronounced in the younger compared to the older participants, F (1, 78) = 6.50, $p < .02$, $\eta_p^2 = .077$. Finally, correlations between IBI1 and performance measures were all non-significant.

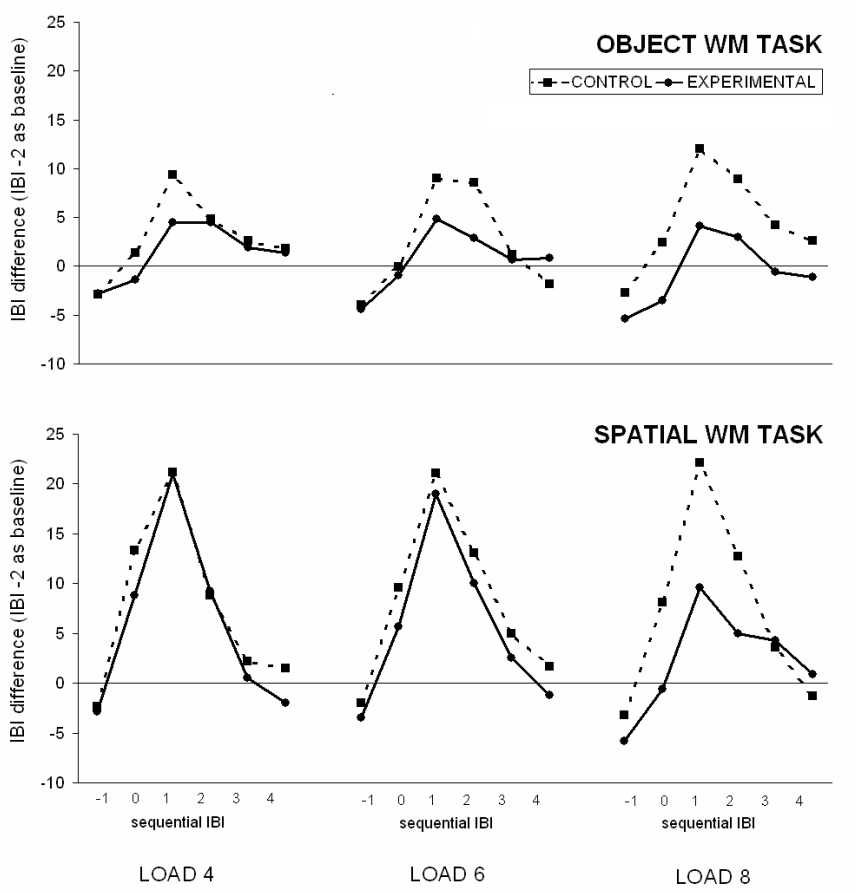


Figure 7.4 *Six IBIs are plotted around the presentation of the stimulus (IBI 0). Average IBI length is plotted for WM loads 4, 6, and 8, in the control and experimental condition for both WM tasks. HR shows anticipatory slowing before stimulus presentation, and an overall relative acceleration in relation to high memory demands.*

Cardiac Response Associated with Feedback Processing.

The IBI response associated with the feedback stimulus is plotted in Figure 7.5. The feedback stimulus is presented during IBI0 and the preceding (IBI-1) and subsequent IBIs (IBI1 and IBI2) are plotted as well. The cardiac response is plotted relative to a pre-stimulus baseline (IBI-2). The left panel of Figure 7.5 presents the IBI response associated with positive or negative feedback following the participant's decision to open a box (i.e., when it was judged that a stimulus was new or a location occupied for the first time). It can be seen that positive feedback is followed by a prompt return to baseline. In contrast, negative feedback is associated with added cardiac slowing (i.e., a lengthening of the IBIs subsequent to the feedback IBI). The right panel of Figure 7.5 displays the IBI response associated with the stimulus following the decision not to open the box (i.e., when it was judged that a stimulus had been seen previously or a location occupied before). Note that in this case the stimulus was always the same (a black screen) and did not provide feedback concerning the correctness of the participant's decision. Thus, in the right panel, 'correct' and 'error' refer to the response, not to information that is provided by the feedback. Yet, it can be seen that acceleratory recovery is postponed on error trials relative to correct trials.

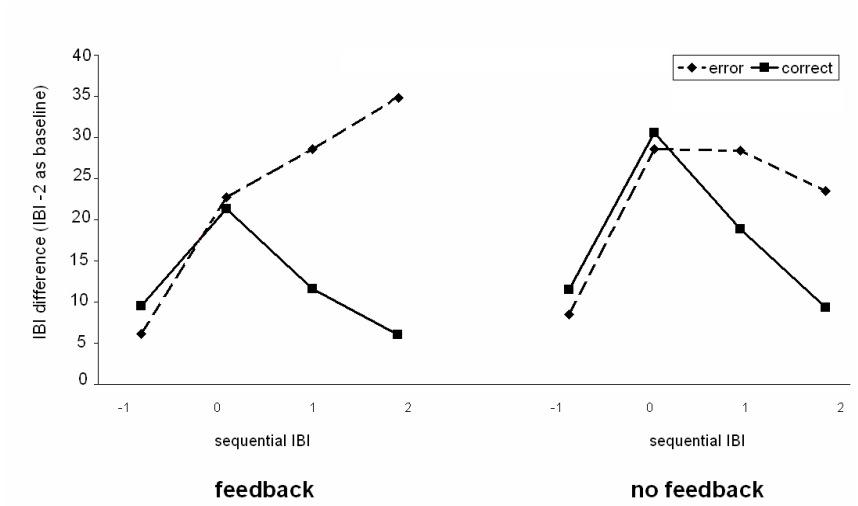


Figure 7.5 *Four IBIs are plotted around the presentation of the feedback (IBI 0). IBI length is plotted for errors and correct responses and for the feedback and no- feedback conditions separately. HR slows following erroneous responses, in both FB conditions.*

The analysis will again focus on IBI 1 (the IBI following the presentation of the feedback), since this IBI was previously found to show the most pronounced effects of the experimental manipulation for feedback processing (Crone, Jennings & Van der Molen, 2004; Crone et al., 2003). The cardiac response associated with feedback processing was statistically examined by performing a repeated measures ANOVA on IBI1 with Age Group (4), as a between subjects factor, and Task (Object/Spatial), Feedback (informative/ uninformative), and Accuracy (correct/incorrect), as within subjects factors. The factor 'Feedback' refers to informative stimuli indicating that the decision to open the box was correct or incorrect vs. uninformative stimuli keeping participants uncertain about the correctness of their decision to leave to box closed. In the latter case, participants had to rely on their own ability to register errors. The ANOVA yielded a significant main effect of Accuracy, F (1, 73) = 21.52, $p < .001$, $\eta_p^2 = .228$. Stimuli following an error delayed acceleratory recovery relative to stimuli following correct decisions. The interaction between Accuracy and Feedback just failed to reach an acceptable level of significance, F (1, 73) = 3.69, $p = .059$, $\eta_p^2 = .048$. This interaction was not altered by Task, $p >. 05$, $\eta_p^2 = .024$, or Age Group, $p >. 05$, $\eta_p^2 = .058$. There was a significant interaction between Task and Feedback, F (1, 73) = 4.25, $p < .05$, $\eta_p^2 = .055$, showing more pronounced cardiac slowing when feedback was informative compared to when it was uninformative but this interaction is difficult to interpret as the higher-order interaction with Accuracy was lacking, $p > .05$, $\eta_p^2 = .024$.

More importantly, the Age Group by Accuracy interaction reached significance, F (3, 73) = 4.37, $p < .01$, $\eta_p^2 = .152$. This interaction is plotted in Figure 7.6. All age groups exhibit the cardiac slowing associated with the stimulus presented following an incorrect response but the slowing increased with advancing age. More specifically, the IBI1 difference between correct and error trials failed to attain significance in the two younger age groups, p's > .15, η_p^2 's < .065, but reached significance in the 11-12 year-olds, F (1, 19) = 4.57, $p < .05$, $\eta_p^2 = .194$, and it was significant in adult participants, F (1, 16)= 14.65, $p < .001$, $\eta_p^2 = .478$. Interestingly, the higher-order interaction between the effects of Age Group, Accuracy, and Feedback fell short of significance, $p = .22$, $\eta_p^2 = .058$, suggesting that children's performance monitoring ability develops slowly for both internal (uninformative feedback) and external (feedback) error detection.

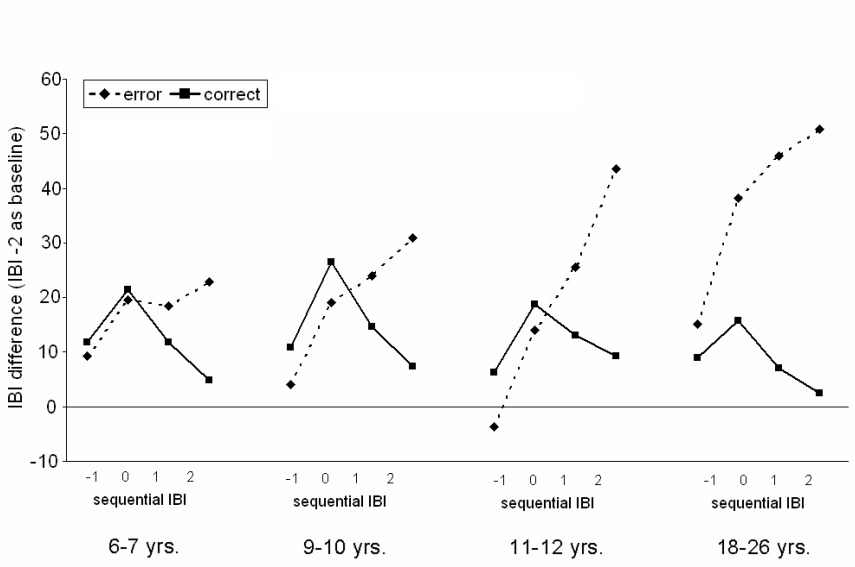


Figure 7.6 *Four IBIs are plotted around the presentation of the feedback (IBI 0). IBI length is plotted for errors and correct responses for each age groups separately. HR slows following performance errors, but this slowing is larger for older age groups.*

7.4 Discussion

The primary goal of the present study was to examine developmental trends in object and spatial WM while avoiding procedural differences between tasks and using control tasks with zero memory demands as a baseline. Age groups performed equally well on the object and spatial control tasks with error rates below 10% for all three series lengths. These data suggest that the assessment of object and spatial WM performance is not confounded by unwanted procedural differences between WM tasks. The pattern of results observed in the experimental conditions of the object and spatial WM tasks show clear differences. The results of the spatial WM task show that all age groups performed equally accurate when the series length was short (i.e., 4 items). Using a WM load of only four items the performance of all age groups equalled the performance on the spatial control task (i.e., error rate less than 10%). However, in all age groups, performance declined when WM load increased, while staying above chance level. Interestingly, this decline was more pronounced for younger age groups. All age groups differed significantly from each other with the exception of the 11-12

year-olds and the adult participants. This finding indicates that spatial WM memory reached mature levels by the end of middle childhood.

The results that emerged from the object WM task show adult error rates for the lowest WM load that were similar to the the results obtained for the spatial task (below 10%). However, in children error rates were higher, the more so when children were younger (in the youngest age group error rates approached 30%). The difference in error rates between the 11-12 years-olds and adults suggest that object WM continues to develop into adolescence.

Why did imposing a WM load demand in the experimental condition of the object WM task have such a detrimental effect on children's performance compared to the effect that a similar manipulation had on their performance in the experimental condition of the spatial WM task, while the performance difference between memory tasks was considerably less pronounced for the adult participants? The data suggest that the object WM task is more difficult than the spatial WM task, adults may have compensated for this difficulty by adopting a verbal strategy. All adults reported to have used a verbal stimulus-coding strategy when performing the object WM task whereas only 10% of the youngest children did, and this finding is consistent with studies on the use of verbal strategies (Palmer, 2000; Pickering, 2001). The analysis aiming at the potential influence of verbal strategy use indicated that participants who used a verbal strategy were more accurate in performing the object WM task than those who did not (84 % vs. 76 %, respectively). Therefore, the differences in performance between age groups is likely to be due to differences in the way participants approached the task, rather than differences in WM capacity per se.

Previously, Hamilton, Coates and Heffernan (2003) reported that developmental trends in object and spatial WM may be obscured by concurrent changes in basic processing speed and/or executive control function (see also: Gathercole, Pickering, Ambridge & Wearing, 2004; Hitch, 2002; Kail, 1992; Kail & Park, 1994; Logie & Pearson, 1997; Pickering, 2001). In order to assess the potentially compromising effect of developmental change in basic processing speed, a standard choice reaction task was adopted from the literature (Van den Wildenberg & Van der Molen, 2004) and included in the present study. This task

yielded the typical age-related increase in the speed and accuracy of responding, consistent with prior studies (Case, Kurland & Goldberg, 1982; Fry & Hale, 2000; Luna et al., 2004; Salthouse, 1992). When basic processing speed was included as covariate in the analysis examining the speed of responding on the object and spatial WM task all significant effects continued to exist. The pattern of significant effects that was obtained for the speed of responding on the WM tasks showed a relatively more protracted development of object WM relative to spatial WM, paralleling the findings observed for accuracy. Interestingly, correlation analyses revealed in all age groups that, as participants were faster on the standard choice reaction task, they responded more accurately on the WM tasks. This finding is consistent with the hypothesis of basic processing speed as a cognitive primitive (e.g., Baltes, Staudinger, Lindenberger, 1999) and the notion that basic processing speed provides a major dimension of individual differences in intelligence rather than developmental change in cognitive capacities (e.g., Anderson, 2001; but see Cerella & Hale, 1994). Hamilton, Coates and Heffernan (2003) observed that developmental differences in executive control function may compromise WM development. Executive control function is a multi-facetted concept that may have several indicators (Diamond, 2002; Miyake et al., 2000; Huizinga, Dolan & Van der Molen, 2006; Welsh et al. 1991; Welsh, 2002). In the present study, a single indicator, derived from the RNG task, was used that has been demonstrated in the past to provide a reliable indicator of executive control function (Baddeley, Emsly, Kolodny & Duncan, 1998; Miyake et al., 2000; Towse & Neil, 1998). Prior studies administering this task to children reported a mild developmental improvement in random generation between 7 years of age and adulthood (Rabinowitz, Dunlap, Grant & Campione, 1989; Towse & Mclachlan, 1999). In the current study, however, the performance on the RNG task failed to discriminate between age groups. Moreover, correlating the RNG index of executive control function with the performance measures derived from the WM tasks failed to reveal any significant associations. However, a single index of executive control function probably does not provide sufficient insight. Therefore, these findings do not speak to the issue of a potential confound between developmental trends in WM and executive control function.

A particular feature of the present study was the use of heart rate changes in order to provide a convergent measure of WM load and to

assess developmental change in feedback and error processing vis-à-vis the WM task demands. The advantage of this measure is that phasic IBIs allow the study of time specific processing (stimulus vs. feedback monitoring) that cannot be observed on the basis of behavior only. The cardiac response showed the typical response associated with the preparation for a significant stimulus and the speeded response to it - anticipatory HR slowing with added deceleration upon the detection and processing of the target stimulus which is then followed by acceleratory recovery associated with the initiation of the motor response (e.g., Somsen, Van der Molen, Jennings & Orlebeke, 1985; for a review: Van der Molen, Somsen & Orlebeke., 1985). We expected that imposing a demand on WM would induce an acceleratory trend, thereby reducing the maximum deceleratory amplitude of the cardiac response. In general, the cardiac results were consistent with this expectation. That is, maximum heart rate slowing was depressed considerably when WM demands were added to the object task and to the spatial task but, in the latter task, only for the highest WM load. The cardiac response did not differentiate between the control and the experimental spatial tasks for low WM loads. The object WM task induced a much stronger acceleratory trend compared to the spatial WM task. This differential effect was smallest for the adult participants. The latter finding could be due to qualitative changes in task performance with advancing age. Future work should examine this possibility by manipulating WM demands across a larger range.

The cardiac response associated with error and feedback processing yielded a particularly interesting finding. As predicted, negative feedback induced added cardiac slowing that was more pronounced with advancing age (e.g., Crone et al., 2003; Crone, Jennings & Van der Molen, 2004). The cardiac slowing to negative feedback has been interpreted to signal a monitoring mechanism that enables improving of performance on subsequent trials (e.g., Crone, Jennings & Van der Molen, 2004). The increase in cardiac slowing to negative performance feedback with advancing age has been taken to suggest that the monitoring mechanism does not reach mature levels until adolescence or even young adulthood (Crone, Jennings & Van der Molen, 2004). The current findings extend the results reported previously by showing that cardiac slowing also occurs following uninformative feedback after an erroneous response. This finding indicates that cardiac slowing is a manifestation of a monitoring mechanism signaling that performance

needs to be adjusted, based on the processing of external feedback or on the internal detection that an error has occurred. In this regard, the cardiac response is similar to the error-related negativity (ERN) that can be recorded over central brain regions (e.g., Holroyd & Coles, 2002; Miltner, Braun & Coles, 1997).

In conclusion, the main finding that emerged from the present study is the separability of developmental trends for object and spatial WM. This finding is consistent with a host of studies suggesting a fractionation of visuospatial WM into separate visual and spatial components (for a recent review Klauer & Zhao, 2004). This finding is consistent also with the developmental literature suggesting that object and spatial WM mature along different trajectories (Hamilton, Coates, & Heffernan, 2003; Logie & Pearson, 1997; Pickering, Gathercole, Hall & Lloyd, 2001). The current HR analysis provided converging evidence by showing that object WM demands contribute to the acceleratory trend of the cardiac response to a greater extent compared to spatial WM demands hereby mirroring and supporting the behavioral findings. Moreover, not only processing demands during the presentation of WM items, but also the subsequent monitoring of performance is related to overall WM performance, and both processes are sensitive to developmental change. These results demonstrate that stimulus processing and outcome monitoring should be studied in parallel and that psychophysiological measures contribute to our understanding of monitoring processes important for WM functioning that cannot be studied on the basis of behavior alone.

8.

Summary and Conclusions

8.1 Introduction

The research described in this thesis aimed to gain insight in risky behavior in adolescence, by examining the development of decision-making in relation to brain development. Chapter 1 describes two existing possible explanations for adolescent risky behavior, the first explanation focuses on the development of cognitive control, and states that adolescents' immature ability to control their impulses may bias them to act risky. The second explanation focuses on emotional/ motivational processes, and suggests that adolescents engage in risky behavior because they respond stronger to the possible rewards associated with risks than children and adults do. This thesis describes experiments that examine developmental changes in three cognitive processes that contribute to mature decision-making, the ability to estimate the probabilities, the ability to weigh potential positive and negative consequences associated with a risk, and cognitive control abilities. Chapters 2, 3, and 7 describe studies on developmental changes in the processes that form the building blocks of more complex decision-making under risk. Chapters 4, 5, and 6 explore the relative contributions of reward sensitivity and cognitive control to decision-making across development. The results from this thesis show that developmental models that try to explain risky behavior in adolescence can gain from knowledge about brain maturation, and from models of age related changes in brain function. In addition, based on these new

insights from developmental fMRI studies, adolescent risk-taking can be explained as the consequence of a difference in the developmental time course of reward related and cognitive control related brain circuitry. An increase in reward sensitivity early in adolescence is proposed to drive teens to take risks; while the ability to control these impulses does not fully develop until late adolescence.

8.2 Development of the neural correlates of basic decision-making processes

Chapter 2 describes an fMRI study in which we examined the ability to estimate probabilities. Participants aged 9 to 12-year-olds and young adults tried to gain as many points as possible by identifying the choice option associated with the highest probability in a two-choice gambling task. On half of the trials, this was an easy task, the probability of choosing the right choice option and winning a point was high (low-risk gambles), on the other half of the trials this choice was more difficult, and the probability of winning was low (high-risk gambles). This was the first developmental fMRI study that examined the neural correlates of cognitive control as well as reward processing. We examined brain activation patterns at the moment that participants made their decision and at the moment they saw the outcome of their choice. Performance differences were minimal, and overall children and adults recruited similar brain regions when performing this task. However, there were differences in the extent of activation between children and adults. At the moment of the decision, the anterior cingulate cortex (ACC) was more active for high-risk gambles than for low-risk gambles, but this difference was larger for 9-12 year olds than for adults. The ACC is considered a key cognitive control region (Miltner et al., 2003; Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004), and this finding suggests that in children the more ambiguous decisions were associated with increased cognitive control. Activation in two other regions which have been linked to cognitive control and decision-making in adults, the dorsolateral PFC (DLPFC) and the orbitofrontal cortex (OFC) were also more active during high-risk relative to low-risk choices, but these regions were not differentially activated for children and adults. When the outcome of gambles was presented, in children, relative to adults, the lateral OFC was more active for losses relative to wins. This difference was taken to suggest that children experienced losses as more aversive than adults.

Further support for the continued maturation of cognitive control during adolescence is presented in Chapter 7. This chapter describes a study on the development of object and spatial working memory (WM) and related feedback processing and performance monitoring. WM and the ability to process feedback and monitor one's performance are key components of cognitive control. In addition to behavioral measures this study describes measures of heart rate (HR) changes, which provided an index of covert cognitive processes. Participants from 4 age groups (6–7, 9–10, 11–12, and 18–26 years old) performed object and spatial WM tasks, in which each trial was followed by feedback. We showed that WM for Object and Spatial information followed dissociable developmental time courses. Spatial WM task performance reached adult levels of performance by age 11, while object WM task performance showed continued change with development during adolescence. This was also seen in improved performance monitoring as reflected in HR slowing elicited by negative performance feedback. This slowing was larger in adults than in children, and did not reach adult levels at age 12, which suggests that performance monitoring continues to change during adolescence.

The second important basic process important in theories on adolescent risk-taking is developmental change in the sensitivity to rewards. In previous studies the motivational circuitry of the brain had been found to be either over-recruited (Ernst et al., 2005; May et al., 2004) or under-recruited (Bjork et al., 2004) in adolescents. These conflicting findings limited our understanding of the reasons behind adolescent risky behavior. One of the confounds of these prior studies is associated with differences in response demands and performance (i.e., leading to strategic differences and making comparisons between age groups difficult). To examine the basic processes in the brain related to anticipation of winning or losing, we performed a second developmental fMRI experiment (Chapter 3) in which we compared 10-12 year olds, 14-15 year olds, and 18-25 year olds using a slot machine task that did not require any active decisions or behavior on the part of the participant. We used this passive experimental task to control for possible confounds of behavioral requirements that could complicate the interpretation of age related differences. The results of this study reveal differences between adolescents and young adults during both the anticipation and the processing of rewards. Received rewards and the anticipation of possible rewards resulted in activation in reward related limbic regions, including the nucleus accumbens and the insula, and

elicited the most pronounced activation in the adolescent brain. In contrast, in adults we found control regions in the PFC to be most active; the OFC was responsive to the omission of rewards in this age group, but not in adolescents. These findings support the hypothesis that reward related regions are more responsive in adolescence.

Taken together, the results from the experiments described in Chapters 2 and 7 support the hypothesis that cognitive control functions continue to develop during adolescence, and that these functions contribute to mature task performance. The result from the experiment described in Chapter 3 suggest that there are fundamental differences in the way that reward related brain regions, the VS in particular, respond in mid-adolescence. These results informed the interpretation of the results from the experiments described in Chapters 4, 5, and 6 in which reward sensitivity and cognitive control both contribute to decision-making, and in which rewards were dependent on performance.

8.3 Development of decision-making under risk; relative contributions of cognitive control and reward sensitivity

Chapter 4 describes a behavioral study in which an adapted version of the paradigm that was introduced in Chapter 2 was used. In this version of the paradigm both the probability of winning and the size of the reward that could be gambled with were manipulated. Participants from 5 age groups (8-9, 11-12, 14-15, 17-18, 25-30 years old) were asked to try to win as many credits as they could by choosing between high-risk/low-probability gambles associated with a higher number of credits, and low-risk/high-probability gambles associated with 1 credit. We tried to control for age related differences in WM capacity that could make the task relatively more difficult for younger participants, by presenting all the information that was needed to make a good decision on every trial. Because of this, no information had to be remembered, or inferred over the course of the task. Earlier studies that have found decision-making skills to improve until late adolescence did not control for this (Crone & Van der Molen, 2004; Hooper, Luciana, Conklin & Yarger, 2004). In contrast to these earlier studies, we found no performance differences between the age groups. This suggests that when all the information that has to be included in a decision is available, the ability to weigh probabilities and potential rewards is mature in children as young as 8 years old. These findings suggest that risky behavior in adolescence is not caused by an immature ability to understand the decisions that have

to be made. However, when decisions are more complex, for example because risk information has to be inferred based on performance feedback, decision-making differences are observed until late adolescence.

As described above psychophysiological measures can gain insight into age related changes in cognitive processes in the absence of differences in behavior. This inspired the study described in Chapter 5 which aimed to test the hypotheses that adolescent decision-making is biased towards taking risks because of an increased sensitivity to possible rewards and immature cognitive control. In this experiment adolescents from three age groups (11-12-year-olds, 14-15-year-olds, and 17-18-year-olds) chose between high-risk and low-risk probabilistic gambles with varying magnitudes of reward. We modified the Cake Gambling Task to enable us to measure heart rate changes. In addition, in this experiment participants gambled with and for a monetary reward. Results showed that risk-taking decreased with age, and the HR data showed that 11-12-year-olds showed a heightened sensitivity to rewards. Age-related changes in HR responses were related to the anticipation of the outcome of risky decisions, not to the evaluation of outcomes. These findings support the hypothesis that a heightened sensitivity to rewards contributes to adolescent risk-taking, and suggest that developmental changes are related to the way adolescents weigh the potential reward when they make a decision. These results fit well with recent theories on adolescent risk-taking, described in more detail in the next section.

8.4 The adolescent brain: Control and emotion out of balance

In Chapter 6 we directly tested the hypothesis that reward related and control related brain regions follow different developmental trajectories in an fMRI experiment. Participants chose between Low-Risk gambles associated with a high probability of obtaining a small reward (1 Euro) and High-Risk gambles associated with a smaller probability of obtaining a higher reward (2, 4, 6, or 8 Euro). We examined brain activation patterns during choice selection and outcome processing in participants from four age groups (pre-pubertal children, early adolescents, older adolescents and young adults). Behavioral findings showed similar behavior across age groups; participants in all age groups were more willing to take a risk when the potential reward was higher. But, with age risk-taking decreased for low rewards. The fMRI results confirmed that High-Risk choices were associated with

activation in VMPFC, whereas Low-Risk choices were associated with activation in lateral PFC. Activation in dorsal ACC showed a linear decrease with age, whereas activation in VMPFC showed an inverted-U shaped developmental pattern, with a peak in adolescence. Gain following High-Risk choices was associated with activation in the VMPFC and VS, and this VS activation peaked in adolescence. These results support the hypothesis that risky behavior in adolescence follows from an imbalance caused by different developmental trajectories of reward related and regulatory brain circuitry. We argue that in future studies adolescent development should be examined in terms of the interplay between subsystems, rather than the development of single mechanisms.

8.5 Conclusions and future directions

The two theoretical accounts presented in Chapter 1 provide different predictions with respect to the development of risk-taking behavior. Behavioral changes in risk taking across development, are sometimes described in terms of a linear decrease as a consequence of increasing cognitive control from childhood to adulthood (Crone & Van der Molen, 2004; Reyna & Ellis, 1994), and sometimes in terms of a peak in adolescence as a consequence of heightened arousal in this developmental phase (Arnett, 1992; Steinberg, 2004). The research presented in this thesis supports the hypothesis that risky behavior in adolescence follows from an imbalance caused by different developmental trajectories of motivational and regulatory brain circuitry (Casey, Getz & Galvan, 2008; Galvan et al. 2006; Steinberg 2008). We argue that recent theories based on these insights from developmental neuroimaging studies provide a framework for understanding risky behavior in adolescence that enables these perspectives to be integrated and can account for the inconsistent findings in the literature. Because risky behavior has been difficult to measure in a laboratory context, psychophysiological and neuroImaging approaches have been particularly valuable. These techniques have helped gain insight into cognitive processes that could not be observed on a behavioral level.

Taken together, the studies in this thesis suggest that adolescents risky behavior is the consequence of increased sensitivity to rewards, paired with immature cognitive control abilities. This conclusion is consistent with recent theories which suggest that reward related and cognitive control related brain systems are complimentary, and together produce

decision-making. The first, evolutionary older, system builds on subcortical structures that have been linked to the processing of emotionally salient information, such as the amygdala and the nucleus accumbens (Ernst *et al.*, 2005; Galvan et al., 2006) and VMPFC, whereas the second, evolutionary younger, system that is important for the control of impulses builds on cortical brain regions, including the lateral PFC/OFC and the ACC (Adolphs, 2003). Age related differences in risk-taking are proposed to be associated with the different patterns of functional development followed by these two brain systems (Casey *et al.*, 2008; Rivers, Reyna & Mills, 2008; Steinberg, 2008). These differential developmental patterns produce a fragile balance between impulses and control in adolescence. We argue that during development both systems contribute to decision-making, but that behavior is dependent on the relative strength of each system in a given situation.

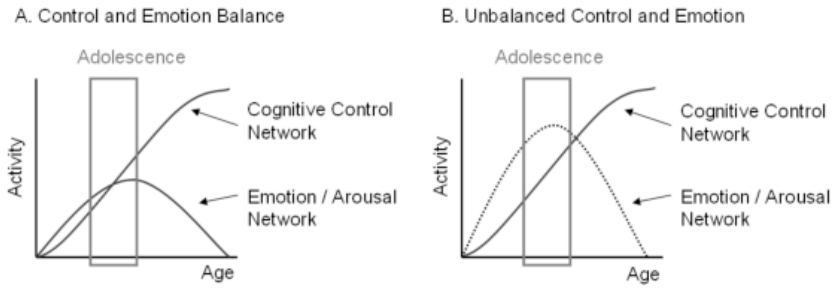


Figure 8.1 *Schematic representation of the relative contributions of cognitive control and emotion/arousal brain systems to decision-making across development. The grey border depicts the difference between both systems in adolescence. Figure A. shows the pattern of brain activation of control relative to emotion arousal regions in neutral conditions,where cognitive control is sufficient to prevent risk-taking; Figure B.shows the same pattern in conditions of increased emotion/arousal, when immature cognitive control abilities cannot prevent risk-taking.*

Figure 8.1A shows a schematic representation of the contribution of both systems as a function of age in an emotionally neutral situation (such as often seen in laboratory tasks). In this situation emotion and cognitive control are balanced, and the model would predict a linear decrease in risk-taking behavior with age, as a consequence of a linear increase in cognitive control abilities. Figure 8.1B shows the situations in which the balance is disturbed, because either the emotion-arousal network is overactive relative to the control network (as in everyday arousing situations for example in the presence of peers), or because the immature cognitive control abilities are insufficient to cope with task

requirements (as for example when complex decisions have to be made). In these situations we predict a peak in risk-taking in adolescence.

Previous studies examining the development of risk-taking in adolescence have used different tasks and methods, and the integration of these methods (including laboratory and real-life assessments, and cognitive, emotional and social task manipulations) is necessary for a full understanding of this phase in development. Adolescence is a unique developmental period that can be characterised by different types of developmental stages. For example, teens can be pre-pubertal, pubertal or post-pubertal, and from a cognitive and social perspective, teens can be referred to as in early, middle, or late adolescence. These distinct stages should be recognized, and studied in order to further disentangle the effects of puberty related hormonal changes and brain maturation.

A recent study illustrates the importance of taking these changes into account, and shows the benefits of using a theoretical approach based on the assessment of cognitive processes that are important in the development of decision-making in terms of their developmental time course and psychophysiological manifestation. During adolescence, friendships change and peers become more and more important. For example, more and more time is spent in the presence of peers than in the presence of parents. It has been suggested that the opinions of peers become more important as well (Harris, 1995). In an experimental study on the influence of peers on adolescent risk-taking, adolescents (13-16-years-old), young adults (18-22-years-old), and adults (24-years-old) played a risk-taking game in the presence of peers and alone (Gardner & Steinberg, 2005). This study showed a disproportionate increase in the number of risky decisions in the presence of peers in adolescents, not adults. It could be that in this task the presence of peers, or the need to fit in, influenced the emotion and arousal brain network in adolescents to such an extent that it led to risk-taking. This illustrates that because of differences in brain function, a situation that would seem risky to adults could be perceived differently by adolescents. For example, because of the presence of friends, the same situation might be perceived as fun by adolescents and scary by adults.

Even though neuroimaging has provided strong evidence for developmental change in brain structure and function and has vastly

increased our understanding of child development, many questions still remain to be answered. One of the major limitations of current fMRI research is the limited ability to explain individual differences in behavior. For example, the results described in Chapter 6 show that differences in risk-taking propensity in the task modulated brain activation in all age groups. Unfortunately, traditional fMRI analyses do not have enough power to draw conclusions about individuals (Logothetis, 2008; Poldrack, 2006). Even though many cognitive functions have been mapped onto specific brain regions, this does not mean that these regions are uniquely responsible for these functions. Conventional fMRI analyses do not allow us to infer from brain activation in a specific region, what cognitive process takes place. Using the traditional analysis methods available today we cannot predict if an adolescent is at a heightened risk based on their brain activation, because activation in a particular region for an individual could be different from the average of the group. Future studies should take these individual differences into account, in particular in the context of studies on development. Individual differences in performance as well as patterns of brain activation are especially large in children and adolescents. The studies described in this thesis, and the potential consequences of adolescent risky behavior underline the importance of further research. We argue that it will be important for future studies to take individual differences into account, and strive for a more detailed understanding of the relation between patterns of brain activation and cognition. The first studies aimed at resolving this issue are currently under way.

Samenvatting en Conclusies

De adolescentie is een fascinerende levensfase. In een relatief korte periode, ongeveer tussen het tiende en twintigste levensjaar, veranderen kinderen langzaam maar zeker in volwassenen. Deze transformatie gaat gepaard met grote veranderingen in het uiterlijk, het psychosociaal en cognitief functioneren en het gedrag. Eén van de veranderingen die de adolescentie kenmerken is een toename in risicovol gedrag. In de context van dit proefschrift definiëren we risicovol gedrag als gedrag dat mogelijke negatieve gevolgen heeft. Dit is een brede definitie en deze negatieve gevolgen kunnen variëren van vervelend tot zeer ernstig. We weten bijvoorbeeld dat adolescenten vergeleken met kinderen en volwassenen, een grotere behoefte aan spanning en sensatie rapporteren. Bovendien piekt het aantal behandelingen op de eerste hulp afdeling van ziekenhuizen als gevolg van bijvoorbeeld ongelukken of overmatig alcoholgebruik in de adolescentie. Het in dit proefschrift beschreven onderzoek had tot doel meer inzicht te krijgen in risicovol gedrag in de adolescentie, door de ontwikkeling van het vermogen beslissingen te nemen in relatie tot de ontwikkeling van de hersenen te bestuderen.

De ontwikkeling van technieken om de structuur en functies van de hersenen in kaart te brengen, zoals *Magnetic Resonance Imaging* (MRI) en *functionele* MRI (fMRI), hebben de laatste jaren bijgedragen aan een grote toename in de kennis over de ontwikkeling van de hersenen. Deze kennis heeft geleid tot nieuwe inzichten in de veranderingen in gedrag gedurende de adolescentie. MRI is een niet-invasieve techniek en daarom ook geschikt voor onderzoek bij kinderen en jongeren. Recent grootschalig longitudinaal MRI onderzoek in de Verenigde Staten naar de ontwikkeling van de structuur van de hersenen van kinderen en adolescenten tussen de 4 en 22 jaar oud heeft aangetoond dat de ontwikkelingsgerelateerde veranderingen in de structuur van de hersenen gedurende de adolescentie omvangrijker zijn dan lange tijd werd gedacht (Gogtay et al., 2004) en dat deze veranderingen niet in alle hersengebieden met dezelfde snelheid plaatsvinden.

De hersenen zijn opgebouwd uit grijze stof (de cellichamen en dendrieten van neuronen) en witte stof (deze bevat de in myeline ingebedde axonen van neuronen en vormt de verbinding tussen de grijze stof gebieden). De witte stof neemt lineair toe tot in de volwassenheid,

terwijl de ontwikkeling van grijze stof volgens een omgekeerde U-vorm verloopt (Giedd et al., 1999). Het aantal neuronen en de verbindingen tussen deze neuronen neemt toe vanaf de geboorte en piekt aan het begin van de adolescentie. Vanaf dit moment neemt de hoeveelheid grijze stof weer af. Neuronen en verbindingen tussen neuronen die niet noodzakelijk zijn verdwijnen en de belangrijke verbindingen worden versterkt.

De ontwikkeling van fMRI heeft het mogelijk gemaakt niet alleen de structuur van de hersenen, maar ook de werking van de hersenen te bestuderen. Omdat fMRI ook geschikt is voor onderzoek bij kinderen en jongeren beschikken we voor het eerst in de geschiedenis over een techniek waarmee we de werkende hersenen in beeld kunnen brengen bij deze leeftijdsgroepen. De laatste jaren is op deze manier het ontwikkelende brein steeds beter in kaart gebracht en zijn belangrijke verschillen ontdekt in de patronen van hersenactiviteit tussen kinderen, adolescenten en volwassenen. In sommige gevallen vertonen kinderen en volwassenen hetzelfde gedrag, maar blijken er wel verschillen te zijn in de processen in de hersenen die ten grondslag liggen aan dit gedrag. Recent fMRI onderzoek, waaronder ook het in dit proefschrift beschreven onderzoek heeft op deze manier bijgedragen aan een beter begrip van risicovol gedrag in de adolescentie.

In Hoofdstuk 1 worden twee in de literatuur heersende mogelijke verklaringen voor risicovol gedrag in de adolescentie beschreven. De eerste verklaring richt zich op de ontwikkeling van cognitieve controle. Met cognitieve controle worden een aantal fundamentele mentale processen bedoeld die ons in staat stellen ons gedrag te controleren en doelgericht te handelen. Van deze processen zoals werkgeheugen (het vermogen informatie in een actieve staat vast te houden en te bewerken), selectieve aandacht (het vermogen onze aandacht te richten op een aspect van de omgeving en tegelijkertijd andere aspecten te negeren) en inhibitie (het vermogen irrelevante gedachten en gedrag te onderdrukken) is aangetoond dat ze pas een volwassen niveau bereiken tijdens de adolescentie. Een toename van cognitieve controle wordt verondersteld te leiden tot een verbetering van het vermogen beslissingen te nemen en hierdoor tot een afname van risicovol gedrag. Deze eerste verklaring veronderstelt dat adolescenten eerder geneigd zijn risico te nemen omdat ze nog onvoldoende in staat zijn om hun gedrag te controleren.

De tweede verklaring richt zich op emotionele/motivationele processen, en veronderstelt dat adolescenten risicovol gedrag vertonen omdat ze vergeleken met kinderen en volwassenen, sterker reageren op de mogelijke positieve gevolgen die met het nemen van een risico geassocieerd zijn.

In dit proefschrift worden experimenten beschreven die aan de ontwikkeling gerelateerde veranderingen in drie cognitieve processen onderzoeken; het vermogen de kans op winst in te schatten, het vermogen de mogelijke positieve en negatieve gevolgen die geassocieerd zijn met een risico tegen elkaar af te wegen, en processen die belangrijk zijn voor cognitieve controle. Hoofdstukken 2, 3 en 7 beschrijven studies naar ontwikkelingsveranderingen in de processen die de bouwstenen vormen van het meer complexe vermogen beslissingen te nemen. Hoofdstukken 4, 5 en 6 beschrijven studies naar deze meer complexe beslissingen en verkennen mogelijke veranderingen in de relatieve bijdrage van de gevoeligheid voor beloning en cognitieve controle bij het nemen van beslissingen gedurende de ontwikkeling van de late kindertijd tot de volwassenheid. De in dit proefschrift beschreven resultaten laten zien dat kennis over de ontwikkeling van de hersenen, en leeftijdsgerelateerde veranderingen in de functie van de hersenen kan bijdragen aan de ontwikkeling van modellen die proberen risicovol gedrag in de adolescentie te verklaren. Zo blijkt bijvoorbeeld dat gebaseerd op nieuwe, met behulp van fMRI studies verkregen, inzichten risicogedrag in de adolescentie kan worden verklaard als het gevolg van een verschil in het ontwikkelingstraject van belonings- en cognitieve controle gerelateerde netwerken in de hersenen. Een toename in de gevoeligheid voor beloningen vroeg in de adolescentie wordt verondersteld tieners aan te zetten tot het nemen van risico's; terwijl het vermogen deze impulsen te controleren pas laat in de adolescentie volledig ontwikkeld is.

De ontwikkeling van de neurale correlaten van basisprocessen die betrokken zijn bij beslissingsgedrag.

Hoofdstuk 2 beschrijft een fMRI studie waarin we 9- tot 12-jarigen en jong volwassenen vroegen kansen in te schatten. In dit experiment vroegen we deelnemers om zoveel mogelijk punten te winnen door steeds de meest waarschijnlijke van twee onzekere uitkomsten te kiezen. We ontwikkelden voor dit doel een taak waarbij deelnemers

taarten te zien kregen die bestonden uit bruine stukken (chocoladetaart) en roze stukken (aardbeientaart) in verschillende verhoudingen. Bij iedere keuze kon een punt worden gewonnen of verloren. Er waren makkelijke keuzes (1 of 2 stukken hadden een contrasterende kleur) en moeilijkere keuzes (3 of 4 stukken hadden een contrasterende kleur). Zowel 9-12 jarige kinderen als jong volwassenen waren goed in staat de meest waarschijnlijke uitkomst te kiezen. We onderzochten bij iedere beslissing de activiteit in de hersenen op het moment dat de deelnemers hun keuze maakten en op het moment dat ze de uitkomst van hun keuze zagen. Dit was het eerste fMRI experiment waarin bij kinderen jonger dan 12 de werking van de hersenen tijdens het nemen van beslissingen voor een beloning werd onderzocht. Bij kinderen en jong volwassenen bleken grotendeels dezelfde hersengebieden betrokken te zijn bij het uitvoeren van deze taak, maar er waren ook verschillen tussen de leeftijdsgroepen. Zo was bij alle deelnemers een gebied in het voorste gedeelte van de hersenen dat geassocieerd is met cognitieve controle, de *Anterior Cingulate Cortex* (ACC), meer actief bij de moeilijke beslissingen dan bij de makkelijke beslissingen. Het verschil in activiteit bij deze verschillende typen beslissingen was echter groter voor de 9-12 jarigen. Dit suggereert dat zij een groter beroep moesten doen op cognitieve controleprocessen bij de moeilijke keuzes dan de volwassenen, zelfs al maakten ze uiteindelijk dezelfde keuze. Twee andere gebieden die in eerdere studies bij volwassenen al betrokken bleken bij het nemen van beslissingen, de Dorsolaterale Prefrontale Cortex (DLPFC) en Orbitofrontale Cortex (OFC) waren ook in deze studie meer actief bij moeilijke keuzes ten opzichte van makkelijke keuzes. Maar de activiteit in deze gebieden verschilde niet tussen kinderen en volwassenen. Er was wel een verschil in hersenactiviteit tussen de leeftijdsgroepen op het moment dat deelnemers de uitkomst van hun beslissingen te zien kregen. Het laterale gedeelte van de OFC was meer actief bij verlies ten opzichte van winst bij kinderen, bij volwassenen was dit verschil er niet. We interpreteerden dit resultaat als een aanwijzing dat kinderen verlies als vervelender ervoeren dan volwassenen.

Verdere ondersteuning voor het idee dat cognitieve controle ontwikkeld gedurende de adolescentie wordt beschreven in Hoofdstuk 7. Dit hoofdstuk beschrijft een studie naar de ontwikkeling van het werkgeheugen voor object- en ruimtelijke informatie. Ook wordt de verwerking van feedback over de prestatie en het monitoren van het gedrag onderzocht. Werkgeheugen, het vermogen feedback te

verwerken en het vermogen het eigen gedrag te monitoren zijn belangrijke componenten van cognitieve controle. In dit experiment bestudeerden we niet alleen het gedrag van de deelnemers, maar onderzochten we ook veranderingen in de hartslag. Deze veranderingen kunnen een indicatie geven van cognitieve processen die niet op grond van gedrag te meten zijn. We vroegen deelnemers uit 4 leeftijdsgroepen (6–7, 9–10, 11–12 en 18–26 jaar) object- en ruimtelijke informatie te onthouden en gaven ze feedback over hun prestatie. Uit de resultaten bleek dat het werkgeheugen voor ruimtelijke informatie sneller ontwikkelt dan dat voor object informatie. Het werkgeheugen voor ruimtelijke informatie van deelnemers vanaf 11 jaar was al even goed als dat van volwassenen, terwijl het werkgeheugen voor object informatie nog geen volwassen niveau had bereikt op 12-jarige leeftijd en nog gedurende de adolescentie verbeterde. De hartslagresultaten lieten zien dat ook het vermogen het eigen gedrag te monitoren toenam gedurende de adolescentie. De hartslag vertraagde nadat deelnemers een fout hadden gemaakt. Deze vertraging wordt gezien als een effect van een toename in de betrokkenheid van cognitieve capaciteit, en deze was groter in volwassenen dan in kinderen. De hartslagreactie had bovendien bij de 11-12-jarigen nog geen volwassen niveau bereikt, wat opnieuw suggereert dat het vermogen de eigen prestatie te monitoren gedurende de adolescentie toeneemt.

Het tweede belangrijke basisproces dat een rol speelt in theorieën over risicogedrag in de adolescentie is de aan de ontwikkeling gerelateerde verandering in de gevoeligheid voor beloningen. Eerdere studies hebben gevonden dan het systeem in de hersenen dat belangrijk is voor het verwerken van beloningen *meer* actief is in adolescenten (Ernst et al., 2005; May et al., 2004), of juist *minder* actief (Bjork et al., 2004). Deze schijnbaar tegenstrijdige bevindingen maken het moeilijker de oorzaken van risicovol gedrag in de adolescentie te begrijpen. De interpretatie van deze resultaten wordt bemoeilijkt door grote verschillen in de gebruikte taken en het beroep dat deze taken doen op de deelnemers. Het is bijvoorbeeld mogelijk dat adolescenten een andere strategie gebruiken dan volwassenen om dezelfde taak uit te voeren, dit zou de vergelijking tussen deelnemers van verschillende leeftijden bemoeilijken. Ook is het mogelijk dat adolescenten een risico als minder groot of een beloning als groter ervaren dan volwassenen. Om fundamentele verschillen in het systeem in de hersenen dat belangrijk is voor de verwerking van beloningen te onderzoeken en tegelijkertijd deze problemen in de interpretatie te voorkomen deden we

een tweede fMRI experiment waarin we een passieve taak gebruikten (Hoofdstuk 3). We vroegen 10-12-, 14-15- en 18-23-jarige deelnemers in een fMRI scanner te kijken naar drie gokkasten. Door op een knop drukten startten deelnemers de gokkasten, en verscheen er achtereenvolgens in iedere gokkast een plaatje. Wanneer alle drie de plaatjes gelijk waren (bijvoorbeeld wanneer drie keer een plaatje van een kiwi verscheen) wonnen zij een klein geldbedrag. Het is belangrijk op te merken dat in deze taak beloningen niet afhankelijk waren van het gedrag of de beslissingen van de deelnemer, en eventuele verschillen in de activiteit in het beloningssysteem in de hersenen dus niet samenhangen met verschillen in gedrag of strategieën. De resultaten van deze studie lieten verschillen tussen adolescenten en jong volwassenen zien tijdens het wachten op mogelijke winst en tijdens het verwerken van uitgekeerde winst. In beide situaties waren gebieden in de hersenen die belangrijk zijn voor het verwerken van beloningen actief. Deze gebieden, waaronder het voorste gedeelte van de Insula, en in de nucleus accumbens (NAcc) in het ventrale gedeelte van het striatum (VS), waren meer actief bij de 10-12 en 14-15-jarige adolescenten dan bij volwassenen. De hersenen van volwassenen reageerden anders. Bij hen vonden we vooral dat gebieden in de prefrontale cortex (PFC) actief waren; de OFC was alleen in volwassenen actief wanneer verwachtte winst uitbleef. Deze resultaten ondersteunen de hypothese dat gebieden in de hersenen die belangrijk zijn voor het verwerken van beloningen actiever zijn in de adolescentie.

Samengenomen ondersteunen de resultaten van de in de hoofdstukken 2 en 7 beschreven experimenten de hypothese dat cognitieve controle functies tijdens de adolescentie nog ontwikkelingsveranderingen laten zien. De resultaten van het in hoofdstuk 3 beschreven experiment suggereren dat er fundamentele verschillen zijn in de manier waarop beloningsgebieden in de hersenen, in het bijzonder in het VS, reageren in het midden van de adolescentie. Deze resultaten vormden de basis voor de experimenten die in de hoofdstukken 4, 5 en 6 zijn beschreven. In deze experimenten waren beloningen wel afhankelijk van het gedrag van de deelnemers en speelden zowel de gevoeligheid voor beloningen als cognitieve controle een rol bij het nemen van beslissingen.

Ontwikkeling van het vermogen beslissingen te nemen in risicovolle situaties; relatieve bijdragen van cognitieve controle en gevoeligheid voor beloningen

Hoofdstuk 4 beschrijft een gedragsstudie waarin gebruik werd gemaakt van een aangepaste versie van het paradigma dat in Hoofdstuk 2 werd gebruikt. In deze versie van de taak werden zowel de kans op winst als de grootte van de beloning waarmee gegokt kon worden gemanipuleerd. We vroegen deelnemers uit 5 leeftijdsgroepen (8-9, 11-12, 14-15, 17-18, 25-30 jaar) te proberen zoveel mogelijk punten te winnen door herhaaldelijk te kiezen tussen een gok met een hoog risico en een lage kans op een groot aantal punten of een gok met een laag risico en een grotere kans op één punt. We probeerden te controleren voor leeftijdsgerelateerde verschillen in werkgeheugencapaciteit die de taak relatief moeilijker zou kunnen maken voor jongere deelnemers door alle informatie die nodig was om een beslissing te nemen op het scherm te tonen bij iedere keuze. Om deze reden was het voor deelnemers niet nodig om voor hun beslissingen relevante informatie te onthouden of ontdekken tijdens het uitvoeren van de taak. In eerdere studies waarin gevonden werd dat het vermogen beslissingen te nemen tot de late adolescentie toeneemt werd hier niet voor gecontroleerd (Crone & Van der Molen, 2004; Hooper, Luciana, Conklin & Yarger, 2004). Anders dan in deze eerdere studies vonden wij geen verschillen in prestatie tussen de leeftijdsgroepen. Dit suggereert dat in een situatie waarin alle informatie die nodig is om een beslissing te nemen beschikbaar is, het vermogen kansen in te schatten en mogelijke beloningen af te wegen al op volwassen niveau is in kinderen van 8 jaar oud. Deze bevindingen suggereren dat risicovol gedrag in de adolescentie niet het gevolg is van een onvermogen om beslissingen en de mogelijke gevolgen daarvan te begrijpen. Maar, wanneer beslissingen meer complex zijn, bijvoorbeeld omdat risico-informatie moet worden geleerd op basis van feedback over het gedrag zijn verschillen in prestatie tot in de late adolescentie te zien.

Zoals hierboven al beschreven kunnen psychofysiologische maten inzicht geven in leeftijdsgerelateerde veranderingen in cognitieve processen wanneer deze niet op grond van het gedrag te meten zijn. Dit gegeven was de aanleiding voor het in Hoofdstuk 5 beschreven experiment. In dit experiment toetsen we de hypothese dat adolescenten eerder risicovolle beslissingen nemen omdat ze gevoeliger zijn voor mogelijke beloningen en omdat ze over onvolwassen cognitieve controle vaardigheden beschikken. Aan dit experiment namen adolescenten uit drie leeftijdsgroepen deel (11-12, 14-15 en 17-18 jaar). We vroegen hen ook in deze studie herhaaldelijk te kiezen tussen een gok met een hoog risico of laag risico en varieerden de hoogte van de

beloning die gewonnen kon worden. We pasten de Taarten Goktaak aan om het mogelijk te maken hartslagveranderingen te meten, en we lieten de deelnemers in dit experiment spelen om Euro's in plaats van punten. De resultaten van deze studie lieten zien dat de bereidheid risico te nemen afnam met leeftijd. Bovendien lieten de hartslagdata een verhoogde reactie op beloningen zien in 11-12-jarigen. Deze leeftijdsgerelateerde verschillen in de hartslagreactie werden gevonden tijdens de anticipatie op de uitkomst van risicovolle beslissingen, niet tijdens het verwerken van die uitkomst. De resultaten van deze studie ondersteunen opnieuw het idee dat een verhoogde gevoeligheid voor mogelijke beloningen bijdraagt aan het nemen van risico's in de adolescentie en suggereren dat leeftijdsgerelateerde veranderingen samenhangen met de manier waarop adolescenten mogelijke beloningen verwerken op het moment dat ze een beslissing nemen. Dit idee sluit aan bij recente theorieën over risicogedrag in de adolescentie die in het volgende gedeelte verder zullen worden besproken.

Het adolescentenbrein: Controle en emotie uit balans

In Hoofdstuk 6 werd de hypothese dat beloningsgebieden en controlegebieden verschillende ontwikkelingstrajecten volgen getoetst in een fMRI experiment. Deelnemers kozen tussen een laagrisico gok waarmee ze een grote kans hadden op het winnen van een kleine beloning (1 Euro) en een hoogrisico gok waarmee ze een kleine kans hadden op een grotere beloning (2, 4, 6 of 8 Euro). We bestudeerden opnieuw de hersenactiviteit op het moment dat de keuze werd gemaakt en op het moment dat de uitkomst werd verwerkt bij deelnemers uit 4 leeftijdsgroepen (8-10, 12-14, 16-17 en 19-25 jaar). Het gedrag van de deelnemers was vergelijkbaar in de verschillende leeftijdsgroepen; in alle leeftijdsgroepen waren deelnemers meer bereid risico te nemen wanneer de mogelijke beloning die daarmee gewonnen kon worden hoog was dan wanneer die laag was. Maar, voor keuzes waarbij de mogelijke beloning klein was, nam de bereidheid een groot risico te nemen af met leeftijd. De fMRI resultaten bevestigden dat hoogrisico keuzes geassocieerd waren met activiteit in de ventromediale PFC (VMPFC), terwijl laagrisico keuzes geassocieerd waren met activiteit in de laterale PFC. Activiteit van het dorsale gedeelte van de ACC liet een lineaire afname met leeftijd zien, terwijl VMPFC activiteit een piek vertoonde in de adolescentie. Winst na hoogrisico keuzes hing samen met activiteit in de VMPFC en het VS, en deze VS activiteit piekte in de adolescentie. Deze resultaten ondersteunen de hypothese dat risicovol

gedrag in de adolescentie voortvloeit uit een disbalans die het gevolg is van verschillende ontwikkelingstrajecten van belonings- en controlegebieden in de hersenen. We stellen dat in toekomstige studies ontwikkelingsveranderingen in de adolescentie als het gevolg van veranderingen in het samenspel van subsystemen in de hersenen en niet als het gevolg van de ontwikkeling van aparte mechanismen zouden moeten worden bestudeerd.

Conclusies en toekomstperspectief

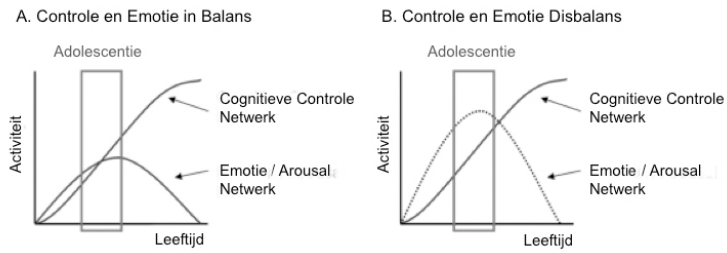
De twee theorieën die in Hoofdstuk 1 zijn beschreven leiden tot verschillende voorspellingen over de ontwikkeling van risicovol gedrag. Het eerste perspectief voorspelt dat risicovol gedrag in de adolescentie een lineaire afname laat zien als gevolg van een toename van cognitieve controle van de kindertijd tot in de volwassenheid, terwijl het tweede perspectief een piek in risicovol gedrag in de adolescentie voorspelt die het gevolg is van een toename van de emotionele/motivationele processen in deze fase van de ontwikkeling.

Het in dit proefschrift beschreven onderzoek ondersteunt de hypothese dat risico gedrag in de adolescentie het gevolg is van een onbalans in de hersenen die voortvloeit uit de verschillende ontwikkelingstrajecten die worden gevolgd door hersengebieden die belangrijk zijn voor het motiveren van gedrag aan de ene kant, en gebieden die belangrijk zijn voor het reguleren van gedrag aan de andere kant. We stellen dat recente theorieën die gebaseerd zijn op neuro-imaging onderzoek bij kinderen en jongeren een raamwerk kunnen vormen waarbinnen verschillende theorieën over risicovol gedrag in de adolescentie kunnen worden verenigd en schijnbaar tegenstrijdige bevindingen in de literatuur kunnen worden verklaard. Omdat het tot nu toe lastig is gebleken risicovol gedrag in een laboratorium context te onderzoeken is onderzoek waarbij gebruik wordt gemaakt van psychofysiologische maten of technieken waarmee het brein in beeld kan worden gebracht erg waardevol gebleken. Deze technieken hebben het mogelijk gemaakt veranderingen in de ontwikkeling te bestuderen die niet op basis van gedrag zichtbaar zijn.

Samengevat, veronderstellen de studies die in dit proefschrift worden beschreven dat risicovol gedrag in de adolescentie het gevolg is van een toename in de gevoeligheid voor beloningen, samen met een langzame ontwikkeling van cognitieve controle. Deze conclusie is consistent met

recente theorieën die veronderstellen dat belonings- en cognitieve controle systemen in de hersenen complementair zijn en samen bijdragen aan het tot stand komen van beslissingen. Het beloningssysteem is evolutionair gezien ouder en bouwt op subcorticale structuren in de hersenen zoals de NAcc, de Amygdala en het ventromediale gedeelte van de PFC, waarvan bekend is dat ze een rol spelen bij de verwerking van emotioneel geladen informatie. Het tweede, evolutionair jongere systeem dat belangrijk is voor de controle van impulsen bouwt op corticale gebieden waaronder de laterale PFC en de ACC. Leeftijdsgerelateerde verschillen in risico gedrag worden verondersteld het gevolg te zijn van de verschillende patronen van functionele ontwikkeling die door deze twee systemen in het brein worden gevolgd.

Deze verschillende ontwikkelingspatronen hebben een kwetsbare balans tussen impulsen en controle in de adolescentie tot gevolg. We stellen dat gedurende de ontwikkeling beide systemen bijdragen aan het nemen van beslissingen, maar dat het uiteindelijke gedrag afhankelijk is van de relatieve sterkte van ieder systeem in een bepaalde situatie. In Figuur 1A is een schematische weergave te zien van de bijdrage van beide systemen gedurende de ontwikkeling in een emotioneel neutrale situatie (zoals we bijvoorbeeld zien in het laboratorium tijdens een experiment).



Figuur 1 *Schematische weergave van de relatieve bijdrage van cognitieve controle en emotie/arousal systemen in de hersenen aan beslissingsgedrag gedurende de ontwikkeling. Het grijze kader geeft het verschil tussen beide systemen in de periode van de adolescentie weer. In Figuur A. is het patroon van hersenactiviteit van controle- ten opzichte van emotie/arousal gebieden te zien in een neutrale context; In dit geval is de cognitieve controle toereikend om risicogedrag te voorkomen. In Figuur B is hetzelfde patroon te zien, in een meer emotionele context. In dit geval kan risicovol gedrag niet worden voorkomen door ontoereikende cognitieve controle.*

In deze situatie zijn emotie en cognitieve controle in balans, en voorspelt het model een lineaire afname in risicogedrag met leeftijd, als gevolg van een lineaire toename in cognitieve controle. In Figuur 1B is

een situatie te zien waarin er sprake is van onbalans, omdat het emotie netwerk relatief actiever is dan het controle netwerk (zoals we vaak zien in spannende situaties buiten het laboratorium), of omdat het onvolwassen controle netwerk ontoereikend is (bijvoorbeeld wanneer beslissingen erg complex zijn). In deze situaties voorspellen we een piek in risicogedrag in de adolescentie.

Eerdere studies naar de ontwikkeling van risicogedrag in de adolescentie maakten gebruik van verschillende taken en methoden, en het integreren van deze methoden (zoals onderzoek in een laboratorium of in het dagelijks leven en de manipulatie van cognitieve, emotionele en sociale factoren in gebruikte taken) is nodig om deze fase in de ontwikkeling volledig te begrijpen. De adolescentie is een unieke periode in de ontwikkeling die op verschillende manieren kan worden gekenmerkt. Tieners kunnen bijvoorbeeld worden getypeerd als pre-puberaal, puberaal of post-puberaal, of vanuit een cognitief en sociaal perspectief als in de vroege, midden of late adolescentie. Deze verschillende fasen zouden moeten worden erkend, en bestudeerd om de effecten van hormonale veranderingen die samenhangen met de puberteit en effecten die samenhangen met de ontwikkeling van de hersenen te kunnen onderscheiden.

Het bestuderen van het ontwikkelingsverloop en de psychofysiologische uiting van cognitieve processen die belangrijk zijn voor de ontwikkeling van het vermogen beslissingen te nemen draagt bij aan het verfijnen van de theorie over ontwikkelingsveranderingen gedurende de adolescentie. Hierbij is het belangrijk rekening te houden met de eerder genoemde verschillende fasen binnen de periode van de adolescentie. Een recente studie illustreert de voordelen van het toepassen van een dergelijke theoretische benadering.

Gedurende de adolescentie veranderen vriendschappen en worden leeftijdgenoten belangrijker. Adolescenten brengen bijvoorbeeld steeds meer tijd door met leeftijdgenoten dan met hun ouders, en de mening van leeftijdgenoten wordt belangrijker (Harris, 1995). In een experiment dat als doel had de invloed van leeftijdgenoten op risicogedrag in de adolescentie te meten, speelden adolescenten (van 13-16 aar oud), jong volwassenen (van 18-22 jaar oud) en volwassenen (24 jaar oud) een risico spel. Ze deden dit alleen, of in het bijzijn van twee leeftijdgenoten (Gardner & Steinberg, 2005). Deze studie liet zien dat er sprake was van een disproportionele toename in het nemen van risico in

aanwezigheid van leeftijdgenoten bij adolescenten, maar niet bij volwassenen. Mogelijk beïnvloedde de aanwezigheid van leeftijdgenoten, of de behoefte er bij te horen, het emotie/motivatie netwerk in de hersenen van adolescenten en leidde dit tot risicogedrag. Deze studie geeft ook een voorbeeld van een situatie waarin verschillen in de manier waarop het brein functioneert kunnen verklaren dat adolescenten dezelfde keuze die door volwassenen als risicovol wordt ervaren anders interpreteren. De aanwezigheid van vrienden leidde er in dit voorbeeld mogelijk toe dat adolescenten de situatie vooral als leuk interpreteerden en volwassenen als gevaarlijk.

Hoewel onderzoek met beeldgevende technieken zoals MRI en fMRI heeft gezorgd voor sterke ondersteuning van het idee dat de structuur en werking van de hersenen verandert gedurende de ontwikkeling, en heeft geleid tot een grote toename van het begrip van de ontwikkeling van kinderen, zijn er nog vele vragen niet beantwoord. Eén van de grootste beperkingen van het huidige fMRI onderzoek is het beperkte vermogen individuele verschillen in gedrag te verklaren. Bijvoorbeeld, de in hoofdstuk 6 beschreven resultaten laten zien dat verschillen in de bereidheid risico te nemen gerelateerd waren aan verschillen in patronen van hersenactiviteit in alle leeftijdsgroepen. Maar helaas zijn de huidige analysetechnieken niet in staat conclusies te trekken over individuen in die groepen (Logothetis, 2008; Poldrack, 2006). Hoewel inmiddels een groot aantal cognitieve functies gerelateerd zijn aan specifieke hersengebieden betekent dit niet dat deze gebieden ook uitsluitend bijdragen aan deze functies. Conventionele fMRI analyses maken het niet mogelijk om op grond van activiteit in een bepaald gebied te zeggen welk cognitief proces plaatsvindt. We zijn dus niet in staat te voorspellen welke adolescent een verhoogd risico loopt op basis van zijn of haar hersenactiviteit. Activiteit in een bepaald gebied voor een individu kan afwijken van het gemiddelde van de groep. In toekomstig onderzoek zal het belangrijk zijn rekening te houden met deze verschillen tussen individuen, met name in de context van onderzoek naar de ontwikkeling. Juist in kinderen en adolescenten zijn individuele verschillen in zowel gedrag als patronen van hersenactiviteit groot. Het in dit proefschrift beschreven onderzoek en de mogelijke nadelige gevolgen van risicogedrag in de adolescentie onderstrepen het belang van verder onderzoek in de toekomst. Dit toekomstig onderzoek zou rekening moeten houden met individuele verschillen en zou moeten streven naar een beter begrip van de relatie tussen patronen van

hersenactiviteit en cognitieve processen. Inmiddels is met dit onderzoek een start gemaakt.

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Propositions

Adolescent risky behavior is the consequence of increased sensitivity to rewards paired with immature cognitive control.

Eight year old children are able to make adult like decisions that require weighing probabilities and potential rewards, this makes it unlikely that adolescents take risks because they don't understand what they are doing.

The finding that the ventral striatum responds more to anticipated and received rewards in mid adolescence than in childhood or adulthood even in the absence of behavior suggests that this reflects a fundamental difference in the way this region functions during this time.

The balance between drive and control that underlies risky behavior in adolescence is dependent on the context.

It is important to educate adolescents about the possibilities they have to shape their brains.

Given the development of the ability to judge probabilities, 14 year olds who say that they are "*never* allowed to do *anything*", and are "*always* misunderstood", probably know that they are wrong.

The development of fMRI has led to revolutionary new insights in child development, and to an enormous number of questions that remain to be answered.

Getting children to lie still is often unjustly seen as the biggest challenge in developmental imaging research.

Future studies should aim to understand the relation between brain function and behavior on the level of individuals.

Curriculum Vitae

Linda van Leijenhorst was born on March 14th 1979 in the city of Middelburg, the Netherlands. She graduated from *Nehalennia Stedelijke Scholengemeenschap Middelburg* in 1998. In 2005 she received a master's degree in psychology from the University of Amsterdam, specializing in developmental psychology. Her master's thesis work was supervised by Prof. Dr. Maurits van der Molen. During the academic year of 2004-2005 she spent six months in Dr. Silvia Bunge's Lab at the University of California, at Davis where she was introduced to developmental fMRI. In 2005 she moved to Leiden University, where she worked towards a PhD with Prof. Dr. Eveline Crone and Prof. Dr. Michiel Westenberg as advisors in the Brain and Development Lab at the department of Developmental Psychology. In August of 2009 Linda joined UCLA's department of Developmental Psychology to work as a postdoctoral researcher in Dr. Adriana Galván's Developmental Neuroscience Lab for which she received a Rubicon fellowship from the Netherlands Organisation for Scientific Research (NWO).

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